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	ROTEASE INHIBITO	, K.S			
57) Abstract	omvides compounds. II	ore part	icularly dipeptide analogs, which bind to retroviral proteases. The full for treating diseases related to infection by retroviruses.		
(57) Abstract The present invention p compounds are inhibitors of r s	provides compounds, netroviral proteases and	nore part d are use	ful for treating diseases related to infection by retroviruses.		
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Background of the Invention

The present invention relates to retroviral protease

10 inhibitor compounds, pharmaceutical compositions thereof, and
a method of treating retroviral diseases therewith, including
a method of treating disease states associated with human
immunodeficiency virus (HIV-1, HIV-2).

13 Retroviridae, are a class of viruses which transport their
15 Retroviridae, are a class of viruses which transport their
genetic material as ribonucleic acid rather than
deoxyribonucleic acid. Also known as RNA-tumor viruses,
their presence has been associated with a wide range of
diseases in humans and animals. They are believed to be the
20 causative agents in pathological states associated with
infection by Rous sarcoma virus (RSV), murine leukemia virus
(MIV), mouse mammary tumor virus (MMTV), feline leukemia
virus (Felv), bovine leukemia virus (BLV), Mason-Pfizer
monkey virus (MPMV), simian sarcoma virus (SSV), simian
25 acquired immunodeficiency syndrome (SAIDS), human Tlymphotropic virus (HTIV-1, -II) and human immunodeficiency
virus (HIV-1, HIV-2), which is the etiologic agent of AIDS

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(acquired immunodeficiency syndrome) and AIDS related complexes, and many others. Although the pathogens have, in many of these cases, been isolated, no effective method for treating this type of infection has been developed.

Retroviral replication occurs only in host cells. Critical to this replication is the production of functional viral proteins. Protein synthesis is accomplished by translation of the appropriate open reading frames into polyprotein constructs, which are processed, at least in part, by a viral protease into the functional proteins. The proteolytic activity provided by the viral protease in processing the polyproteins cannot be provided by the host and is essential to the life cycle of the retrovirus. In fact, it has been demonstrated that retroviruses which lack the protease or contain a mutated form of it, lack infectivity. See Katoh et al., Virology, 145, 280-92(1985), Crawford, et al., J. Virol., 53, 899-907 (1985) and Debouk, et al., Proc. Natl. Acad. Sci. USA, 84, 8903-6(1987). Inhibition of retroviral protease, therefore, presents a method of therapy for retroviral disease.

The use of isosteric replacements has been disclosed as a strategy for the development of protease inhibitors for HIV-1. European Patent Applications EP-A 337,714, EP-A 357 332, EP-A 346 847, EP-A 342 541, EP-A 352 000, EP-A 393 445 and EP-A 434 365 are representative, and are incorporated herein by reference. These references disclose dipeptide analogs of the natural polyprotein substrates of retroviral proteases. As discussed therein, these dipeptide analogs bind selectively and competitively to satisfy the selective and competitively to satisfy the selective and competitively to satisfy the selective and competitively the selective and proteases. As alsoussed the conformal proteases; bind selectively and competitively to retroviral proteases; made and constant proteases; also also the carbon-carbon however, the protease is unable to cleave the carbon-carbon bond presented to it instead of the scissile amide bond of the natural substrate. Thus, such compounds are useful for inhibiting viral replication by inactivation of the protease. The incorporation of heterocyclic elements in the P3' and P4' substrate positions of compounds containing a dipeptide isostere has been disclosed by deSolms et al., J. Med. Chem., 34, 2852 (1991). However, these compounds can be less than desirable for obtaining optimal drug delivery in mammalian

organisms, particularly in humans. Some of these compounds can also have a less than desirable serum half-life, and therefore duration of action, because they contain amide bonds in relatively high proportion, and thus are prone to metabolic degradation, hepatic clearance, or other elimination mechanisms.

There exists a need for novel compounds which inhibit retroviral protease activity, and a need for compounds which possess desirable pharmacokinetic properties for good drug delivery and metabolic stability for good serum half-life and duration of action. Such pharmaceutical uses provide therapies for retroviral diseases in mammals, especially in humans, which have been heretofore difficult to treat.

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SUMMARY OF THE INVENTION

The present invention provides compounds, hereinafter represented as formula (I), which bind to retroviral proteases. These compounds are inhibitors of retroviral proteases and are useful for treating diseases related to infection by retroviruses.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

The present invention additionally provides a method for treating retroviral disease, comprising administering to a mammal in need thereof an effective amount of a compound of formula (I): (134) 35 . (35 36 46 . (3)

30 (CMD) O COLUMN DETAILED DESCRIPTION OF THE INVENTION

and to Jose The compounds of the present invention are illustrated by formula (I):

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R1 and R3 are each independently Q, Q-C1-6alkyl, Q-C2-6alkenyl, Q-C2-6alkynyl or C1-6alkyl substituted by one to five fluorine atoms, each optionally substituted by R23; Q is H, C3-6cycloalkyl, C5-6cycloalkenyl, Ar or Het R2 is H or OH;

R5 is R6-NR11 or R102NR11; or set or settor is Appeared to the first to the left.

R6 is

X is NR^{11} , O or S:

 R^7 is Q, Q-C₁₋₆alkyl or Q-C₂₋₆alkenyl;

 ${\rm R}^{8}$ and ${\rm R}^{9}$ are each independently H, OH, halo, ${\rm NO}_{2}$, ${\rm COR}^{12}$, CF₃, Ar, C_{1-6} alkyl- R^{15} , or $R^{17}(R^{18}R^{19}C)_m$, or together form a fused C2-4alkylene, aryl or heteroaryl moiety;

 R^{10} is $A-(B)_{n}-;$

R11 is H or C1-4alkyl;

R12 is R7, OR7, NR7R11 or an amino acid or amino alcohol;

B is an amino acid; the liquon will be measured 20

A is H, Ar, Het, R17 (R18R19C) m, Ar-W, Het-W or R17 (R18R19C) m-W, or phthaloyl each optionally substituted by one to three groups chosen from R15 or C1-6alkyl-R15;

W is C=0, OC (=0), NR¹¹C(=0), SC(=0), NR¹¹C(=S), SO₂,

 $NR^{11}SO_2$ or P(=0) (OR^{22});

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R15 is H, nitro, C₁₋₆alkoxy, C₁₋₆alkylthio, O(C=O)R16, C=OR²², CO₂R²², CON (R¹⁶)₂, N(R²²)₂, NHC (=N) NH-A, I, Br, Cl, F, OR10, or OH, provided that when R15 is a substituent of the carbon adjacent to W, R15 is not halogen or OH when W is OC(=O) or NHCO;

R16 is H or C1-6alkyl;

 ${
m R}^{17}, {
m R}^{18}$ and ${
m R}^{19}$ are independently: i) H, ${
m R}^{15}$ or C_{1-4} alkyl, C_{2-6} alkenyl, phenyl, naphthyl, C_{3-6} cycloalkyl or Het, each optionally substituted by one to three R15 or

joined together to form a phenyl, naphthyl, C3-6cycloalkyl or Hetiring, or iii) R¹⁷ is as above and R¹⁸ and R¹⁹ together are corecard =0;) of her happy was the many resembles and R¹⁸ and R¹⁹ together are

 $R^{22} \text{ is}_{\text{H,9}} C_{1-6} \text{alkyl, phenyl or phenyl-} C_{1-4} \text{alkyl;}$ $R^{23} \text{ is}_{\text{-X'-(CH_2)}} \text{qNR}^{24} \text{R}^{25}, \text{X"[((CH_2)_rO)_s]} \text{R}^{26},$

The Roll Response of the C1-4alkyl; and continued a substituted with C1-4alkyl;

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s is 1-6 and r is 1-3 within each repeating unit s;

(3) Sing X" is (CH₂, NR', O, S, SO or SO₂;

OR²⁴ and R²⁵ are i) C₁₋₆alkyl, optionally substituted by

- OH, C1-3alkoxy, or N(R*)2, ii) the same or different and joined together to form a 5-7 member heterocycle containing up to two additional heteroatoms selected from NR, 0, S, SO, SO2, said heterocycle optionally substituted with C1-4alkyl, iii) aromatic heterocycle, optionally substituted with
- 20 C1-4alkyl-or N(R')2; Layer ore of the hard a greater

walk!cis H or C1-4alkyl; over the given a given a give A

 R^{26} is H, C_{1-4} alkyl, $C(=0)R^{27}$, $C(=0)U[(CH_2)_mO]nR^4$, $P(=0)(OM)_2$, CO_2R^{27} , $C(=0)NR^{27}R^{28}$, where M is a mono or divadelent metal ion, and U is NR' or O;

R²⁷ is C₁₋₆alkyl or Ar, optionally substituted with one or more hydroxy, carboxy, halo, C₁₋₃alkoxy, CONR'₂, NR'₂, CO₂R', SO₂NR'₂, CH₂NR₂, NR'COR', NR'SO₂R', X"[(CH₂)₂O]₈R' or CH₂X"[(CH₂)₂O]₈R'; District All All Yelds

OF R²⁸ is H, C₁-6alkyl or together with R²⁷ forms a 5-7

30 [Ymembered heterocycle or a 6 membered heterocycle containing a heteroatom selected from N, O and S;

· m is 1-4; and

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or a pharmaceutically acceptable salt thereof.

35 view Also included in this invention are pharmaceutically vacceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be

many covalently bonded carriers which release the active parent drug according to formula (I) inluivo. beside

rormula (I) is intended to encompass all unique
nonracemic stereoisomers which may occur due to the presence
of asymmetric carbon atoms in the molecule. Such compounds
may occur as pure enantiomers or diastereomers or as a
mixture of individual stereoisomers. The definition of any
substituent moiety which may occur more; than once in formula
(I) is independent of any other occurrence combinations of
substituents and/or variables are permissible only if such
combinations result in stable compounds:

Compounds of this invention which include acyclic double bonds may be present in either the cis (Z) or trans (E) geometrical configuration with respect to any two

15 substituents. The same of the control in the substituents.

when X is NH, it will be appreciated that the character is an imidazole which can undergo the tautomerization. All tautomerics forms: of the imidazole are within the scope of this invention.

Suitably R¹ and R³ are C₁₋₆alkyl, Ar-C₁₋₆alkyl, S Ar-C₂₋₆alkenyl, Ar-C₂₋₆alkynyl, C₁₋₆alkyl optionally substituted by one to five fluorine atoms or benzyl substituted in the 4-position by R²³ Preferably R¹ is benzyl and R³ is benzyl, 4-hydroxybenzyl or phenylpropenyl.

Suitably R⁷ is H, C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl or benzyl. Preferably R⁷ is C₁₋₆alkyl. Isopropyl is most preferred.

Suitably R⁸ is H, C₁₋₆alkyl, COR¹², NO₂ or Br. Preferably R⁸ is H.

Suitably R⁹ is H₁, NO₂, Br₁, COR¹², CF₃, Ar₁, C₁-6alkyl or C₁-6alkyl-R¹⁵, wherein R¹² is H₁, C₁-6alkyl, Ar₁, OC₁-6alkyl, NH₂, and R¹⁵ is OH. Preferably R⁹ is H₂ or COR¹².

Suitably B is Ala or Val. Preferably m is 0 and B is absent, which is absent, which is absent.

Suitably A is Het, R17 (R18R19C) m-W, Ar-W or Het-W.

- Suitably R17, R18 and R19 are H, or C1-4alkyl, Het or Ar
- - Suitably W is C=O, OC (=O), NHC (=O), NHC (=S), or SC (C=O).

 Suitably R¹⁷ (R¹⁸R¹⁹C)_m is Ar-CH₂, Ar, Het, Het-CH₂,
- 10) C1-6alkyl or C3-6cycloalkyl optionally substituted by one to three groups selected from R¹⁵. Suitably R¹⁵ is OH. When R¹⁷ or (R¹⁸R¹⁹C) are Het or Ar, Het is suitably quinolinyl, pyridyl, imidazolyl, thiazolyl, tetrahydrothiopyranyl or tetrahydropyranyl, and Ar is phenyl.
 - Suitably R²³ is hydroxy-C₁₋₄alkoxy, C₁₋₄alkoxy-C₁₋₄alkoxy, or -O(CH₂)₂NR²⁴R²⁵, wherein R²⁴ and R²⁵ are are a

or .6-membered heterocycle, such as morpholino.

In one preferred embodiment W is C=O. *** ** *** ***

- " i) " In another preferred embodiment W is OC (=0).
- C5-6cycloalkylOC(=0) substituted by one or two OH or CH2OH

 groups.
 - Representative compounds of this invention are:

 (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
 - 25 amino-6-phenyl-N-[1'-isopropyl-1'-(4-aminocarbonyl-thiazo-2-yl)]methyl-hexanamide;
 - (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-

 - 30 (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
 - amino-6-phenyl-N-(1'-imidazo-2-yl)methyl-hexanamide
 - -i hydrochloride; was a relative to the second of the seco
 - -'; amino-6-phenyl-N-[1'-methyl-L'-(imidazo-2-yl)] methyl-
 - 35 hexanamide hydrochloride; (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-[1'-benzyl-1'-(imidazo-2-yl)]methyl-hexanamide hydrochloride;

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(2R, 4S, 5S, 1'S) -5- (carbobenzyloxy) amino-4-hydroxy-N-(1'-
                                isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
                                                                                                               Settebly A is Me. of the Co
                               hexanamide:
                                (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                5 isopropyl-1'-(4,5-dimethyl)imidazol-2-yl]methyl-6-phenyl-2-
                       P phenylmethyl-hexanamide; of special maker by a collection
                               (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                              isopropyl-1'-(N'-methyl)imidazol-2-yl]methyl-6-phenyl-2-
                         phenylmethyl-hexanamide: w("81, 234) 132 vices a
                              (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy'N-(1'-
                             isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3->= (3-
                           phenylpropargyl) hexanamide; $ 10 300 010 (50 550) uc
                             (2R, 4S, 5S, 1'S) -5- (benzyloxyethoxycarbonyl) amino-4-hydroxy-N-
                             (1'-isopropyl-1'-imidazol-2-yl)methýl-6-phenyl-2-10:
                          phenylmethyl-hexanamide:
                            (2R, 4S, 5S, 1'S) -5- (methoxycarbonyl) amino-4-hydroxy-N-(1'-
                           isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
                          hexanamide;
                                                                                                              in the second second of the second se
                           (2R, 4S, 5S, 1'S) -5-(ethoxycarbonyl) amino-4-hydroxy-N-(1'-
(C20 ) isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
                         hexanamide:
                                                                                                                                               of the form that the read by the sec
                          (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
                        isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2-
                       propenyl) hexanamide; "seelings, assemblings (0.50, 5, 22, 32)
     25 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                       isopropyl-1'-(4-nitroimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide; who are section 200,200,000,200
                       (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
                      ethyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
                    hexanamide; 25 42 14 14 14 15 at made-S-(2° E (20 (2) (2))
                       (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
                    propyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
                                                                           more the mode of the english and gother ($) by $2,500, and
                 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                    isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6-phenyl-2-
                   phenylmethyl-hexanamide; discrete and property of the state of the sta
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(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1!-(4,5-dibromoimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide; but (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1!-(4-methylimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide;
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isopropyl-1'-(4-trifluoromethylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide;

10 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-methyl[vd: N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2phenylmethyl-hexanamide;

isopropyl-1'-(4-carbomethoxyimidazol-2-yl)]methyl-6-phenyl-2-

15 phenylmethyl-hexanamide; (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-

-5. isopropyl-1!-(4-methylcarbonylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide;

(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-

isopropyl-1'-(4-phenylcarbonyl-imidazol-2-yl)]methyl-6-*:
phenyl-2-phenylmethyl-hexanamide;

(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'isopropyl-1'-(4-formylimidazol-2-yl)] methyl-6-phenyl-2phenylmethyl-hexanamide;

25 (2R, 4S; 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4-(hydroxymethyl)-imidazol-2-yl)] methyl-6phenyl-2-phenylmethyl-hexanamide;

(2R, 4S, 5S; 1'S) -5- ((tetrahydrothiopyran-4-yl)) oxycarbonyl) - amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-

30 phenyl-2-phenylmethyl-hexanamide; 4444 (2R,4S,5S,11S)-5-((tetrahydro-4H-pyran-4-yl)) oxycarbonyl)-

phenyl-2-phenylmethyl-hexanamide;
(2R, 4S, 5S, 1'S) -5-(4-picolinyloxy) amino-4-hydroxy-N-(1'-

35 more isopropyl-1 - imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide; water water the large and the same of the same

"न के राजन विकार विश्व देवा देवा होते हैं है। अने देवा है कि एक देवा है कि एक कि कि है है कि पा कर है है है है

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La service data del conse
    (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
    isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(4,4,4-
     trifluorobut-1-yl) hexanamide ; was hearly herighted
    (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
     isopropyl-1'-(4-((1RS)-1-hydroxyethyl)-imidazol-2-yl)]methyl-
     6-phenyl-2-phenylmethyl-hexanamide; *xxxii-iydinalig odd
    (2R, 4S; 5S, 1'S) = 5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-(1-
     methyl)propyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-
     phenylmethyl-hexanamide; againg fyn am (yn adag Sry'y aff).
10 (2R, 4S, 5S, 1'S) -5-(propylaminocarbonyl) amino-4-hydroxy-N-[1'-
     isopropyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-
     hexanamide;
                                    sees girethyl-hexai anti-us
     (2R, 4S, 5S, 1'S)-5-(4-hydroxybutanoyl)amino-4-hydroxy-N-(1'-
    _isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-juca-ask
    phenylmethylhexanamide;
                               · (基础) (16) (16) (17-4) 或数据数"代数数值"
    (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(benzyloxy-
    carbonyl) valylamino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-
                                  $1.00 ton constrainment products
     yl) methyl-hexanamide;
     (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(N-acetylvalyl)-
    amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-yl)methyl- 68
                           to the transfer the specific transfer in the specific of
    hexanamide;
    (2R, 4S, 5S, 1'S)-5-[(imidazol-2-yl)methyloxycarbonyl]amino-4-
    hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
    phenylmethyl-hexanamide;
                                    the factor of the control of
25 (2R, 4S, 5S, 1'S, 1"RS) -5-((1"-(imidazol-2-yl)-2"-methyl) - es
    propyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
    imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide;
     (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
   isopropyl-1'-(4-(imidazol-2-yl)imidazol-2-yl)]methyl-6-
    phenyl-2-phenylmethyl-hexanamide; the type of the second of the phenylmethyl-hexanamide;
     (2R, 4S, 5S, 1'S) -5- (1-oxo-thian-4-yl) oxycarbonyl) amino-4-
    hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
    phenylmethylhexanamide; a masked to the standard very and a
   (2R, 4S, 5S, 1'S) -5- ((tetrahydrosulfonylpyran-4- (4.44))
35 ...yl) oxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
    yl) methyl-6-phenyl-2-phenylmethylhexanamide; #5 heranssoni
    (2R, 4S, 5S, 1'S) -5-((1, 1-dimethyl-2-(benzyloxycarbonyl-)
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glycyloxy) ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-

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imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide
                            (2R, 4S, 5S, 1'S)-5-((1, 1-dimethyl-2-glycyloxy) ethoxycarbonyl)-
                         amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
          5 syphenyl-2-phenylmethyl-hexanamidedihydrochloridesalt;
                            13, (2R, 4S, 5S, 1'S) -5-((1-acetyl)amino-4-hydroxy-N-(1'-isopropyl-
                                   1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide;
                                    (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
   · : : : : : : : : : isopropyl-1!imidazol-2-yl) methyl-6-phenyl-2-(4-:::)
                                 benzyloxyphenylmethyl) hexanamide; when we are on white
                 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
   isopropyl-1;imidazol-2-yl)methyl-6-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-2-(4-phenyl-
                 (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-hydroxy-2-
                  15 phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2-
           toble wyl]methyl-hexanamide; if the group of the con-
                 (2R, 4S, 5S, 1'S) -5- ((isopropylthiol) carbonyl) -amino-4-hydroxy-
   The Mark W2-phenylmethyl-6-phenyl-N-[1-isopropyl-1'-imidazol-2-
  Taysongoyl]methyl-hexanamide; and avoiding a second to the second
                                  (2R, 4S, 5S, 1'S) -5-[3-(1H-imidazol-2-yl)-3-hydroxy-4-
                 • [] - methylpentylamido] -4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
   tobesame y1) methyl-6-phenyl-2-phenylmethyl-hexanamide; Casteria
          .. N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
                 25 phenylmethyl-hexanamide;
              - 11-2R, 4S, 5S, 1'S)-5-(t-butylaminocarbonyl) amino-4-hydroxy-N-(1'-
               3-6, isopropyl-1,-imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
                                  (2R, 4S, 5S, 1'S) -5- (methylaminocarbonyl) -;
                  · 11. amino-4-hydroxy-N-(1!-isopropyl-1!-imidazol-2-yl)methyl-6-
    -2-30 mg/phenylmethyl-hexanamide; the transfer of the transfer of the second se
                                 (2R, 4S, 5S, 1'S)-5-phenylaminocarbonyl) amino-4-hydroxy-N-(1'-
- S- (Lycomisopropyl-1!-imidazol-2-yl) methyl-6-phenylmethyl-hexamide;
                 (2R, 4S, 5S, 1'S) -5-N-(propylaminocarbonyl) amino-4-hydroxy-N-
                                 (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
or of 35 the hexamide; indexposite in the first property in the first constitution of the first 
                 _c_,(2R,4S,5S,1'S)-5-(n-propylaminothiono)amino-4-hydroxy-N-
                                 (1'isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
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2R, 4S, 5S, 1'S) -5-(isopropylaminocarbonyl) -amino-4-hydroxy-N-
                            (1'-isopropyl-1'-imidazol-2-yl)methŷl-6-phenylmethyl-
- (fyror is hexamide; (i) the land of the first section in the first section is
     (2R, 4S, 5S, 1'S) -5- (aminocarbonyl) amino-4-hydroxy-N-(1'-
                 5 isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-hexamide;
- (2R, 4S, 5S, 1'S) -5-(6-quinolinylmethyloxy-carbonyl) amino-4-
                          hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
           phenylmethyl-hexanamide; 15 350 1-3 -2 (251 20 20 350 50)
                           (2R, 4S, 5S, 1'S) -5- (benzoyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
                          imidazol-2-yl)methyl-6-phenylmethyl-hexanamide; 2004 01
              10
                :- (2R, 4S, 5S, 1'S)-5-(2-furylcarbonyl) amino-4-hydroxy-N-(1'-
                          isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
                           (2R, 4S, 5S, 1'S) -5- (4-methoxybenzoyl) amino-4-hydroxy-N- (1'-
                          isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
                          (2R, 4S, 5S, 1'S)-5-benzylcarbonyl) amino-4-hydroxy-N-(1'-1f
              15
                          isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
                          (2R, 4S, 5S, 1'S) -5-(4-hydroxybenzoyl) amino-4-hydroxy-N-(1'-
                          isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
                          (2R, 4S, 5S, 1'S)-5-(cinnamoyl) amino-4-hydroxy-N-(1'-isopropyl-
                          1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
             20
                          (2R, 4S, 5S, 1'S) -5-(2-hydroxybenzoyl) amino-4-hydroxy-N-(1'-
                          isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
                          (2R, 4S, 5S, 1'S) -5-(imidazoyl-4-yl-acetyl) amino-4-hydroxy-N-
                          (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
                                                                                                         16 Mannary in Fridding growing
                         hexanamide;
                         (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                   isopropyl-1'-(4-carbomethoxyethylimidazol-2-yl)]methyl-6-
                         (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                         isopropyl-1'-(4-carboxamidoimidazol-2-yl)]methyl-6-phenyl-2-
                 phenylmethyl-hexanamide; thest and the state of the state
                        (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl)-2-
                       thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
                        yl))methyl-hexanamide; the of the second of the literature of the 
                        (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl) -2-
                       thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
                   of yl)) methyl-hexanamide; (40 % de as a contactique agent a)
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-13) -- -- (2R, 4S, 5S, 1, S) -2-phenylmethyl-4-hydroxy-5- (5-propyl-2-
            -i.rd ..thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
                                    yl))methyl-hexanamide; and
               ... (2R, 4S, 5S, 1'S) -5- (nicotinyl) amino-4-hydroxy-N-(1'-isopropyl-
            -3-5, (1'-imidazol-2-yl) methyl-6-phenylmethyl-hexamide.
                                                      Another group of preferred representative compounds are:
      with the (2R, 4S, 5S, 1'S) -5-[di(hydroxymethyl)-methoxycarbonyl] amino-4-
 -! -!-! Lyned: hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-
                                  phenylmethyl-hexanamide; which is a second of the second o
           -1110 (2R, 4S, 5S, 1 S) -5- (1, 1-dimethyl-2-acetoxyethoxycarbonyl) amino-
                                   4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
                                  phenylmethyl-hexanamide; half which me ten open and
        -P- og by (2R, 4S, 5S, 1'S)-5-((1, 1-dimethyl-2-hydroxy)ethoxy-
       -Salva carbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(4-alaya
                                  isopropylcarbonyl-imidazol-2-yl))methyl-6-phenyl-2-
   is to be phenylmethyl-hexanamide dihydrochloride salt;
                           :0(2R, 4S, 5S, 1'S) -5-((1S)-1-methyl-2-hydroxyethoxycarbonyl)-
                  Y amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
       phenyl-2-phenylmethylhexanamide; went a second of the seco
        120 (2R, 4S, 5S, 1'S) -5-((1R)-1-methyl-2-hydroxyethoxycarbonyl)-
          -A . ( amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-
              phenyl-2-phenylmethylhexanamide;
     ... (2R, 4S, 5S, 1'S) 5- (1-hydroxymethyl-cyclopentyloxycarbonyl)-
                               .amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
   read 25% iphenyl-2-phenylmethyl-hexamide; here the recommendation
                  .m. od (2R, 4S, 5S, 1h.S) -5- (1, 1-dimethyl-2-hydroxyethoxycarbonyl) amino-
   edition of hydroxy-N-(1!-isopropyl-1!-imidazol-2-yl)methyl-6-phenyl-2-
     West phenylmethyl-hexanamide hydrochloride; was wanted
       رد مراج المحتور (2R, 4S, 5S, 1<sup>N</sup>S) -5- (hydroxyethoxycarbonyl) amino-4-hydroxy-N-
from 30 % (1'-isopropyl-la'-imidazol-2-yl) methyl-6-phenyl-2-
                               phenylmethylhexanamide; and
etc fir gg. E(2R,4S,5S,1,S)-5-(2-hydroxy-1-methylethoxycarbonyl) amino-4-
Wife the hydroxy-N-(1:-isopropyl-1:-imidazol-2-yl)methyl-6-phenyl-2-
       and it phenylmethylhexanamide demonstrate the property of the same
                                   .: Win More preferred representative compounds are:
                               (2R, 4S, 5S, 1; S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
      no transamino-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl)) methyl-
      rd vigo hexanamide hydrochloride; whose the same fair of a control of the same fair of the
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(2R, 4S, 5S, 1'S) -5-(isopropoxycarbonyl) amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethylhexanamide;
(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-

isopropyl-1'-(4-isopropylcarbonyl-imidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide; greyre redicted

(2R, 4S, 5S, 1'S)-5-(1, 1-dimethyl-2-hydroxyethoxycarbonyl) amino4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2phenylmethyl-hexanamide hydrochloride; and greyre

10 V (2R,4S,5S,1'S)-5-(hydroxyethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-i->
phenylmethylhexanamide; and imministrative segments (2R,4S,5S,1'S)-5-(2-hydroxy-1-methylethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2phenylmethylhexanamide.

The term "alkyl" refers to a straightfor branched chain alkyl radical of the indicated number of carbon atoms.

"C1-4alkyl" as applied herein is meant to include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl; "C1-6alkyl" includes additionally pentyl, isopentyl, 2-methylbutyl, 1-methylbutyl, 2-ethylpropyl, neopentyl, n-hexyl 2,2-dimethylbutyl, 2-methylpentyl, and the like.

"Alkoxy" refers to an alkyl group of the indicated number of

25 "Alkylthio" refers to an alkyl group of the indicated number of carbon atoms attached through a bridging sulfur atom.

carbon atoms attached through a bridging oxygen atom.

The term "substituted alkyl" as used herein is meant to include C1-6alkyl, Ar-C1-6alkyl, if Het-C1-6alkyl, C2-6alkenyl, Ar-C2-6alkenyl, Het-C2-6 alkenyl, C3-6cycloalkyl-C1-6alkyl,

30 C3-6cycloalkenyl-C1-6alkyl or C1-6alkyl substituted with acyl or hydroxyl.

"Alkenyl" refers to a straight or branched hydrocarbon chain of the indicated number of carbon atoms, which contains one or more carbon-carbon double bonds at any stable point

along the chain, such as ethenyl, propenyl; butenyl, propenyl; butenyl, propenyl; and the like.

"Alkynyl" refers to a straight or branched hydrocarbon chain of the indicated number of carbon atoms which contains

. The gradual carbon-carbon triple bond at any stable point along the This is an chain, such as ethynyl, 2-propynyl, 2-butynyl, 4-pentynyl, fig. as as 2-methyl-3-propynyl, hexynyl and the like. 345 The term "acyl" means R12-CO, wherein R12 is H, 5 C₁₋₆alkyl, Ar-C₁₋₆alkyl, Het-C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C2-6alkenyl, Het-C2-6alkenyl, C3-6cycloalkyl- C1-6alkyl, C5_6cycloalkenyl-C1_6alkyl, OH, NHR13, wherein R13 is H, Light on C1-6alkyl, Ar-C1-6alkyl, Het-C1-6alkyl, C2-6alkenyl, Ar-C2-6alkenyl, Het-C2-6alkenyl, C3-6cycloakyl-C1-6alkyl, or . 10: C3-6cycloalkyl, or C5-6cycloalkenyl-C1-6alkyl; or an α-amino acid or an α-amino alcohol bonded at the nitrogen. sinyone ise a "Cycloalkyl" refers to a saturated ring group of the indicated number of carbon atoms. "C3-7cycloalkyl" includes * file is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 15 'cycloheptyl' "Cycloalkenyl" refers to a saturated ring group of the indicated number of carbon atoms, having at least one endocyclic carbon-carbon double bond. "C5-7cycloalkenyl" includes cyclopentenyl, cyclohexenyl and cycloheptenyl. "Aryl", abbreviated as Ar, refers to phenyl or naphthyl, optionally substituted with one to three halo, OH, OR10, C1-6alkyl, C1-6alkoxy, C1-6alkylthio, C1-6alkylamino, CF3, ACCOMMENT amino, NO2, carboxy, C1-4alkylcarbonyl, aminocarbonyl, The description of C1-6alkyl-Het, C1-6alkoxy-Het, C1-6alkyl-phenyl, C1-6alkoxyphenyl, C1-6alkyl-, C1-6alkoxy-, HetC1-6alkyl-, HetC1-6alkoxy-, 25 phenylC1-6alkyl-, phenylC1-6alkoxy- or phenyloxy. As used herein except where noted, the term "heterocycle", abbreviated as "Het", represents a stable 5second in to 7-membered monocyclic or a stable 7- to 10-membered bicyclic heterocyclic ring, which is either saturated or 1 0030 unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may ive optionally be oxidized, and the nitrogen heteroatom may but optionally be quaternized, and including any bicyclic group 35.: in which any of the above-defined heterocyclic rings is fused - to a benzene ring! The heterocyclic ring may be attached at Dust any heteroatom or carbon atom which results in the creation

of a stable structure, and may optionally be substituted with

one to three halo, OH, alkyl, alkoxy, alkyl-Het, alkoxy-Het, alkyl-phenyl, alkoxy-phenyl... Examples of such heterocyclic elements include piperidinyl, piperazinyl, -2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furyl, pyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzoxazolyl, thiamorpholinyl!sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Heteroaryl refers to a heterocycle which has aromatic character (eg., characterized by delocalized electron resonance and the ability to sustain a ring current).; Pyridine, imidazole, thiazole, furan and oxazole are examples of heteroaryl rings. fart and the

"Amino acid" means the D- or L- isomer of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine or trifluoroalanine.

In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in Eur. J. Biochem., 158, 9 (1984). Usually lipophilic amino acids are preferred for the moiety B, for instance, Val, Ala, Leu and Ile. It will be understood that a linkage B-O refers to an oxygen atom bonded to the carboxyl group of an amino acid, and that a B-N linkage indicates a nitrogen atom bonded to the carboxyl group of an amino acid, as; in an amide bond.

"Amino alcohol" refers to an amino acid in which the carboxyl group has been reduced to a methylene hydroxy group.

Certain chemical names are abbreviated herein for the sake of convenience. Boc refers to the t-butoxycarbonyl radical. Cbz refers to the carbobenzyloxy radical. Bzl refers to the benyzl radical. Ac refers to acetyl. Ph: refers to phenyl. BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. DCC refers to dicyclohexylcarbodiimide: DMAP refers to

dimethylamin-opyridine. DMSO refers to dimethylsulfoxide. HOBT refers to 1-hydroxybenzotriazole. NMM is Nmethylmorpholine. DTT is dithiothreitol. EDTA is ethylenediamine tetraacetic acid. DIEA is diisopropyl

ethylamine. DBU is 1.8 diazobicyclo[5.4.0]undec-7-ene. DMSO is dimethylsulfoxide. DMF is dimethyl formamide; Lawesson's reagent is 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4diphosphetane-2,4-disulfide and THF is tetrahydrofuran. refers to hydrofluoric acid and TFA refers to trifluoroacetic 10 acid.

The compounds of formula (I):

The source of (I) water you at me at the 15 wherein \mathbb{R}^4 is CO-NR CHR6R7, \mathbb{R}^5 is $\mathbb{R}^{10}\mathbb{R}^{11}\mathbb{N}$ -, and \mathbb{R}^1 , \mathbb{R}^2 , \mathbb{R}^3 and R6 are as defined in formula (I), are prepared by: and orall (a) coupling a compound of the formula (II):

with every line we have a section of
$$R^{5}$$
 and R^{5} and R^{5} are the every line where R^{6} are the every line R^{6} and R^{6} are R^{6} and R^{6} are the every line R^{6} and R^{6} are R^{6} and R^{6} are the every line R^{6} and R^{6} are R^{6} and R^{6} are the every line R^{6} and R^{6} are R^{6} and R^{6} and R^{6} are R^{6} and R^{6} are R^{6} and R^{6} and R^{6} are R^{6} and R^{6} are R^{6} and R^{6} are R^{6} and R^{6} are R^{6} and R^{6} and R^{6} are R^{6} and R^{6} and R^{6} are R^{6} and R^{6} are R^{6} and R^{6} are R^{6} and R^{6} and R^{6} are R^{6} and R^{6} and R^{6} are R^{6} and R^{6} and R^{6} are R^{6} and R^{6} are R^{6} and R^{6} are R^{6} and R^{6} are R^{6} and R^{6} are R^{6} and R^{6} and R^{6} are R^{6}

with a compound of formula (III):

od officaordgo you adnage will me HR'N-CHR6'R7'

Holife , SAME been west . Short is man . (III) , as a rome is done in the where R1', R2', R3', R5', R6' and R7' are as defined for

formula (I) with any reactive groups protected, Prl is H or a hydroxyl protecting group, and L' is OH or a leaving group;

or lyoungdowned to generate the rest of the following in (in coupling, a compound of the formula (IV):

with a compound of the formula (V):

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CL

HOE'S restained to 12 marter (V) and the second second of the second was second to the second was second or second o

wherein A' and B' are as defined in formula (I) with any reactive groups protected; or and a second bound (Al)

(c) coupling a compound of the formula (VI)

with a compound of the formula (VII) : 300 000 362 3

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A'-L'

(VII)

and,

- 2) if appropriate, a coupling agent; and
- 3) removing any protecting groups and
- 15 4) forming a pharmaceutically acceptable salt thereof. 15

 The coupling reactions may be accomplished by activating

the substrate with a reactive functional group in situ or prior to the coupling reaction, such that it is reactive with an amino group. For instance, acids may be converted to acid chlorides, bromides, activated esters or anhydrides, or by adding a coupling reagent. Coupling agents are well known in the art for activating a functional group in situ,.

Exemplary of such agents are DCC and other carbodismides,

DMAPEC, BOP and PPA. These coupling agents may optionally be used with other reagents, such a HOBT, NMM and DMAP, which may facilitate the reaction.

Suitable leaving groups, L', are those which are displaceable by an amino group, such as bromo, chloro, a substituted acyl (eg. trifluoroacetyl, bromobenzoyl, nitrobenzoyl) or a substituted phenol (eg. 4-nitrophenol) and the like. If L' is OH, so that A-OH is an acid, it will be appropriate to use a coupling agent as hereinbefore described.

For instance:

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ver home and to R17 (R18R19C) m, L1 may be a bromo, chloro, iodo or an alkyl or arryl'sulonate. Other are to be

When A is R¹⁷ (R¹⁸R¹⁹C)_m-W, Ar-W or Het-W, and W is C=O, 5 a A-L' may be at carboxylic acid halide, activated ester or adanhydride, or a carboxylic acid in the presence of a coupling agent. Methods for preparing such compounds are well known.

All agent When W is OC=O, A-L' may be a chloro- or bromo-formate,

1 or an activated carbonate. Haloformates may be prepared by

10 creacting the appropriate alcohol with phosgene or carbonyldibromide. Activated carbonates may be prepared by the appropriate alcohol with a suitable carbonate such as bis (4-nitrophenyl) carbonate.

RA TO DECOMMENT Wais: SO2, A-L' may be a sulfonyl halide; which may

11 15 Whe prepared from the corresponding sulfonic acid.

When Wis SC=0, A-L may be a halothioformate, which may be prepared from a carbonyldihalide and an appropriate mercaptan.

When W is PO(OR²²), A-L' may be a phosphonyl halide,

20 Which may be prepared from the corresponding phosphonic acid.

Compounds wherein A is R¹⁷(R¹⁸R¹⁹C)_m-W, Ar-W or Het-W,

and W is NR'C=O are ureas, and may be prepared by reacting a

compound of formula (VII) with an isocyanate of the formula

R¹⁷(R¹⁸R¹⁹C)_m-NCO, Ar-NCO or Het-NCO, in a suitable solvent

such as methylene chloride, optionally with heating.

Compounds of formula (III), wherein X is nitrogen, are imidazoles and may be prepared according to Scheme 1, wherein Pr² is a removeable amino protecting group, and R⁷, R⁸ and R⁹ correspond to R⁷, R⁸ and R⁹ as defined for formula (I), or a group which may be converted into R⁷, R⁸ or R⁹, with any reactive groups protected.

Scheme 1

The amino aldehydes are generally known or are prepared by methods well known in the art, for instance, by reduction of a suitable α-amino acid ester with dissobutylaluminum hydride. Further reaction of the aldehyde with a gem dialdehyde, or diketone, and ammonia yields the desired imidazole. Alkylation and further modification of the substituent groups of the imidazole are within the skill of the art. Such a method and other methods for preparing

imidazoles are disclosed, for instance, by Baldwin et al., J.

10 Med. Chem., 29, 1065 (1986), Angew Chem: Int., 22, 560 1

(1983); and Hughey et al., Synthesis, 1489 (1980). 183

Alternately, acyl imidazoles may be prepared by coupling an α-amino acid to a substituted 4-amino-isoxazole, and

subsequent reduction and base catalyzed rearrangement as
disclosed generally by Reiter, L.A., J. Org. Chem., 52, 2714
(1987). Intermediate compounds of formula (VIII) are a part
of this invention. Preferably, R⁷, is C1-6alkyl and more
preferably C3-6alkyl. Suitably, R⁸ and R⁹ are H, NO₂, Br,
COR¹², CF₃, Ar, C₁-6alkyl or C₁-6alkyl-R¹⁵, wherein R¹² is H,

C1-6alkyl, Ar, OC1-6alkyl, NH₂, and R¹⁵ is OH or a protected

hydroxyl group. Preferably R9 is H or COR12. ACC.

Compounds of formula (III), wherein X is sulfur, are thiazoles and may be prepared according to Scheme, 2, wherein L' is a suitable displaceable group.

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Scheme 2 to sign works

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Accordingly, a thioamide is reacted with a ketone or aldehyde. Thioamides are commonly prepared from carboxamides by reacting the corresponding carboxamides with a reagent such as Lawessons reagent, as disclosed, for instance, by Hamada et al., Tet. Lett., 931 (1991). Suitable displaceable groups are those which are displaced by a sulfur nucleophile,

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such as chloride, bromide, iodide, mesylate, p-tolunesufonate groups, and the like.

Compounds of formula (III), wherein X is oxygen, are oxazoles and may be prepared according to Scheme 3 from common amino acids.

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Scheme 3

10 Typically the acid may be coupled to an appropriately substituted amino alcohol by common techniques, as described above, and cyclized by treatment with thionyl chloride to yield an oxazoline, as described by Meyers et al., J. Org. Chem., 43, 1372 (1978). Oxidation of the oxazoline, such as described by Evans et al., J. Org. Chem., 44, 497 (1979), yields an oxazole.

The compounds of formula (II), (IV) and (VI), wherein R² is H, are prepared, for instance, according to Scheme 4.

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ිසි විටිකය ක්රොය (පෙරි වියක (VIII) ද මුල් පැරණි ඇති වෙයට පොලා පැරණි පතුන සිත්විත මුතු විතිස්ත් වියක් සිතුම්මේ සිට සිතුවේම සුට විවිධයේ ලිය නොවා පාරා ප්රාදේශයේ

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Scheme 4

Other methods for preparing protected 5-amino-4-hydroxy-15 2,5-disubstituted-pentanoate esters and acids, and the corresponding Y-lactones, are well known and are disclosed, for instance, in Szelke et al., U.S. Patent 4,713,455, Boger et al., U.S. Patent 4,661,473, EP-A 0 352 000, Evans et al., J. Org. Chem., 50, 4615 (1985), Kempf, J. Org. Chem., 51, 3921 (1986), Fray et al., J. Org. Chem., 51, 4828 (1986), Halladay et al., Tett. Lett., 24, 4401 (1983), Wuts et al., J. Org. Chem., 53, 4503 (1988), DeCamp et al., Tett. Lett., 32,1867 (1991), and Szelke et al., WO 84/03044, all of which are incorporated herein by reference.

15 The compounds of formula (II), (IV) and (VI), wherein R^2 is OH, are also prepared by methods common in the art such as those disclosed in U.S. Patent 4,864,017, and Thaisrivongs et al., J. Med. Chem., 30, 976 (1987).

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Compounds of formula (I), wherein R5 is R6-NR11, are prepared according to Scheme 5, Scheme 6 or Scheme 7:

Scheme 5

$$H_2N$$
 H_2N
 H_2N
 H_2N
 H_2N
 H_2N
 H_2N
 H_3
 H_3
 H_4N
 H_4
 H_5
 H_5
 H_5
 H_7
 $H_$

ກ່າວ ກ່ອງ ເສດ ... ຄະເມື່ອການ ພາກ ການ **Scheme 6**

Scheme 7

wherein R1'-R4', R7' and R8' are as defined in formula (I)

with any reactive groups protected, L' is a leaving group,

15' such as halogen, and Pr1 is a hydroxy-protecting group

note and 15' such as halogen, and Pr1 is a hydroxy-protecting group

Compounds wherein R^4 is R^6NR^{11} are prepared in an analogous manner from a compound of formula (IX):

Suitable protecting groups for the amino, hydroxyl, carboxylic acid, mercaptan group, and reagents for deprotecting these functional groups are disclosed in Greene et al., PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, Second Edition, John Wiley and Sons, New York, 1991. Deprotection indicates the removal of the protecting group and replacement with an hydrogen atom. In particular, suitably substituted acetyl, benzyl and silyl groups are useful for protecting the hydroxyl group. The acetyl group is commonly removed by reacting the compound with a base, such as an alkali metal hydroxide, in a mixture of an alcohol and water. The silyl group, such as trimethyl silyl, dimethyl-t-butyl silyl, and t-butyl-diphenyl silyl may be removed by a fluoride reagent, such as a tetra-alkyl ammonium fluoride, or by acid hydrolysis. The benzyl group may be removed by catalytic hydrogenation.

Suitable protecting groups for the amino group are those disclosed by Greene et al., as indicated previously. The benzyloxycarbonyl and t-butoxycarbonyl groups are especially useful amino protecting groups.

The present invention includes pharmaceutically acceptable acid addition salts. Acid addition salts of the present compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic or methanesulfonic. The acetate salt form is especially useful. If the final compound contains an acidic group, cationic salts may be prepared. Typically the parent compound is treated with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation. Cations such

cas Na+, K+, Ca++ and NH4+ are examples of cations present in pharmaceutically acceptable salts. Certain of the compounds Office of the land and of mothercompounds of the present invention selectively bind 55 to retroviral proteases in the same manner as the virally "coded natural substrates of the proteases and compete with these substrates for protease, thereby serving to inhibit viral replication by blocking the formation of crucial viral proteins from polyprotein precursors by the protease, and 10 hence, to inhibit disease progression in vivo. The present compounds achieve such beneficial therapeutic effect because they contain unique structural features which impart Violated desirable pharmacokinetic properties to the compounds. One such property is long duration of action. We have found that substitution of a heterocycle, especially imidazole, in the putative P21 position of the present compounds affords compounds which retain good enzyme binding affinity, good antiviral activity, a favorable duration of action and water solubility for good drug delivery. 20 When a compound of the present invention is administered to an animal infected or potentially infected with a retrovirus, viral replication is inhibited and hence disease progression is retarded. Inasmuch as the amino acid 180 to sequences of the protease binding and peptide bond cleavage sites of various retroviruses appear to be highly conserved, an inhibitor is likely to be broadly active against more than one retrovirus. Also, DNA viruses which are dependant upon virally encoded proteases, such as the hepatitis virus, may also be susceptible to such treatment. The such deliver The compounds of formula (I) are used to inhibit retroviral replication, and are useful in treating mammals, 'particularly human patients, who are infected with susceptible retroviruses and require such treatment. The method of treating a retroviral disease in a mammal, particularly a human, comprises internally administering (e.g. orally, parenterally, buccally, trans-dermally, leads rectally or by insufflation) to said mammal an effective

amount of a compound of formula (I), preferably dispersed in

a pharmaceutical carrier. Dosage units of the active ingredient may be selected by procedures routine to one skilled in the art, and are generally in the range of 0.01-50 mg/kg. These dosage units may be administered one to ten times daily for acute or chronic infection we Preferably the compound is administered at a level of 1-10 mg/kg, two to four times daily. No unacceptable toxicological effects are indicated when compounds of this invention are administered in the above noted dosage range.

The present invention also provides a method of treating disease states associated with HIV infection or Acquired Immune Deficiency Syndrome (AIDS), comprising administering an effective amount of a compound of formula (I), preferably dispersed in a pharmaceutical carrier.

Beneficial effects may be realized, by co-administering, individually or in combination, other anti-viral agents with the protease inhibiting compounds of the present invention.

Examples of anti-viral agents include nucleoside analogues, phosphonoformate, rifabutin, ribaviran, phosphonothicate oligodeoxynucleotides, castanospermine, dextran sulfate, alpha interferon and ampligen. Nucleoside analogues, which include 2',3'-dideoxycytidine(ddC), 2',3'-dideoxyadenine(ddA) and 3'-azido-2',3'-dideoxythymide (AZT), are especially useful. AZT is a preferred agent. Suitably, pharmaceutical compositions comprise an anti-viral agent, a protease inhibiting compound of the present invention, and a pharmaceutically acceptable carrier.

This invention is also a pharmaceutical formulation which comprises a compound of formula (I) and a pharmaceutically acceptable carrier. Pharmaceutical acceptable carrier are well known in the art and are disclosed, for instance, in SPROWL'S AMERICAN PHARMACY, Dittert, L. (ed.), J.B. Lippincott Co., Philadelphia, 1974, and REMINGTON'S PHARMACEUTICAL SCIENCES, Gennaro, A. (ed.), Mack Publishing Co., Easton, Pennsylvania, 1985.

Pharmaceutical compositions of the compounds of the present invention, or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral

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6.37 caladministration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable 5 % diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate "Solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or 10 nebulizer for insufflation. It may be desirable to add excipients such as ethanol, polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, 15 tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, soy bean oil, peanut oil,

20 Solive oil, glycerin, saline, ethanol, and water.

with a 0042 Solubilizing agents, such as dimethylsulfoxide, ethanol or 51 formamide, may also be added. Carriers, such as oils, optionally with solubilizing excipients, are especially The Posuitable. Oils include any natural or synthetic non-ionic

25 Swater-immiscible liquid, or low melting solid, which is the dissolving lipophilic compounds. Natural oils,

fill to Ysuch as triglycerides are representative. In fact, another

see interest of this invention is a pharmaceutical composition comprising a compound of formula (I) and an oil.

30 30 Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Solubilizing agents, such as dimethylsulfoxide or formamide, may also be added. The carrier may also include a sustained release material

35 besuch as glyceryl monostearate or glyceryl distearate, alone . Soon if of or with a wax. The amount of solid carrier varies but,

The state preferably, will be between about 20 mg to about 1 g per

dosage unit. The pharmaceutical preparations are made

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following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

A suitable dosage form for oral administration has been prepared by dissolving the peptide of Example 1 (312.5 mg) in dimethyl sulfoxide (1 mL) and diluting to a concentration of 12.5 mg/mL with soybean oil. A suitable dosage form for intravenous administration has been prepared by dissolving the compound of Example 1 (0.02 g) in dimethyl sulfoxide (1 mL) and diluting to 20 mL with a 70% propylene glycol/30% ethanol solution.

For rectal administration, a pulverized powder of the compounds of this invention may be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository. The pulverized powders may also be compounded with an oily preparation, gel, cream or emulsion, buffered or unbuffered, and administered through a transdermal patch.

The pharmacological activity of the compounds of this
invention may be demonstrated by enzyme assays to determine
the inhibitory activity of the retroviral protease, by in
vitro cellular-based assays to determine the ability of the
compounds to penetrate cells and inhibit viral replication,
and by pharmacokinetic assays to determine oral
bioavailability, drug half-life and clearance. These assays
are well known in the art.

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ENZYME ACTIVITY TO THE STANDARD THE RESERVE OF THE STANDARD THE STANDA

The ability of the compounds of this invention to inhibit the HIV-1 protease enzyme may be demonstrated by using the assay disclosed by Dreyer et al., Proc. Natl. Acad. Sci., U.S.A., 86, 9752 (1989), Grant et al., Biochemistry, 30 8441 (1992), and EP-A 352 000. The Ki for the compounds of

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this invention are in the range of 1 nM to 5 µM. Preferred
       compounds, have, Ki's of less than 100 nM.
  cofunding space program in a count yearns of 0. Lag. (sooled
  O to ginfectivity o kan a bis's of for he wild less is second
    6.5. and the ability of the compounds of this invention to gain
 entry to cells infected with the human immunodeficiency
    wirus, and to inhibit viral replication in vitro may be
  'da to demonstrated using the assay described by Meek et al.,
  As at 3 Nature, 3343,690 (1990), and Petteway et al., Trends
 nt blode Pharmacol. Sci. 12, 28; (1991) . The IC50 for the compounds of
     and this invention are in the range of 0.1 to 10 µM.
  they have become the did not on the hattened ample more
    End of CYTOTOXICITY, All pulpers, now now hold of the
  the Religious Cytoitoxicity is assessed by both direct microscopic
         examination of trypan blue stained cells (T-lymphocytes) and
 yd form by the treated culture stability to metabolize the
     And Stetrazolium, salt; XTT- (2,3-bis[2-methoxy-4-mitro-5-tg
... to sulfophenyl]-2H-tetrazolium-5-carboxanilide; sodium, salt), to
    Los (its formazan, dye ), The XTT assay allows determination of the
         50% toxic concentration of compounds for the cell/virus
add lo (Isystem used. to think the transfer are ex-
  and the true and services and the first services and the analysis of
  no determacokinetics for the \chi -form \chi - \chi
 : noithage sa Dual jugular cannulated Sprague Dawley rats weighing 200
        to 250 g were utilized in all studies. All dosing and sample
  .00 92 (collection was done from conscious rats. Before dosing, a
 #01. 16 time: 0: blood: sample, 0:300; μL, was: drawn using one of the
        catheters. Utilizing the second catheter the rats were dosed
 slovel dintravenously. At 1,5,10,30,60,90,6120, 150, 180 and 210
5 4:30 min after dosing, 300 µL blood samples were drawn. To The rats
10 middledosed@orally were administered the compound by rutilizing a 22
  and gauge gastric gavage needle and samples were drawn sat 30, 60,
 c1 - 111-90/2 120/31240/2 360/2 480/2 600/2 720 and 1440 min. The blood
     . samples were placed-in precooled tubes containing 30 mL of
    35g sodium citrate and centrifuged in a microfuge. The plasma
 or my was transferred then snap frozen on dry ice, and stored at
 edu de a70°C:until analyzed. Histophen bandle en le bet den
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randment beart a estimate that the designed by the designed

Standard stock solutions (1 mg/mL) of inhibitor was prepared in 100% DMSO. A dilution series of the stock solutions were prepared in a total volume of 0.1 mL (pooled normal rat plasma/DMSO) to yield final concentrations of 0 and 0.5-120X the Ki of the inhibitor. All dilutions were performed in triplicate. These spiked plasma solutions were extracted with 0.5 mL acetonitrile by vigorous vortexing, . followed by centrifugation for 10 min. An aliquot (0.4 mL) of the supernatant was removed and dried in Eppendorf tubes 10 31 10 using a Speed-vac. The (resulting residue was) redissolved in DMSO. The inhibition of the HIV-leprotease activity was assayed as follows. An aliquot of the extracted sample was: added to a 50 µL mixture containing 1X MENDT buffer, 1 mM substrate and incubated at 37°C < 10 min of The reaction was ina 15: then initiated by the addition of HIV-1 protease and continued at .37°C for an additional 15 min, then quenched by the addition of TFA (0.5% final concentration) realnitial 67 (The rates were determined for each standard curve as the fraction est to not remaining enzymatic activity (vi/vo) at each inhibitor 20 concentration, in which vo is the velocity of the IC 68 (inhibitor concentration)=0 sample. Assuming that all of the original inhibitor in the spiked samples was extracted, the values of vi/vo were plotted versus inhibitor concentration 90 take of the original extracted sample and fitted to the equation: to un 25 to vi/vo=[AEt - It - Kit+ (Ki-AEt-It) 0.5]/(2AEt), p 08 1 out - et B At in which Et is the total enzyme concentration at time zero, Ki is the apparent inhibition constant and A is the fraction o to the or coftactive enzyme. The process of the polar that a subdivisuo Ex vivo animal plasma samples containing unknown levels of protease inhibitor were prepared and analyzed as described for the standard curve described above? The concentration of inhibitor in these samples was then determined using the Ki and A parameters from the fitted standard curve according to the following equation: $c(I_t = AE_t[1 - (v_i//v_0)]) + K_f(v_0/v_i)$. 5 35 35 of The data was plotted as the natural (log (ln) of the 1: looplasma concentration versus time on semilogarithmic paper to generate the plasma concentration-vs-time curves? Using the IV data, the apparent terminal rate constant was determined

form the linear regression analysis of the plasma
concentration-vs-time curve. The elimination half-life
(t1/2) was derived by dividing ln 0.5 (=0.693) by the
terminal rate constant. The area under the plasma

5 concentration-vs-time curve (AUC) was determined by using the ln/log trapezoidal rule. C_{max} represents the maximal plasma concentration and t_{max}, the time following drug administration at which C_{max} was observed. Both values were estimated by inspection of the plasma concentration-vs-time curve. Total plasma clearance (CL) was calculated by

dividing the dose by the AUC. The fraction of the oral dose provided available to the systemic circulation (the bioavailable fraction, F) was determined by the equation: F = [AUC_{po}/DOSE_{po}] x [DOSE_{iv}/AUC_{iv}].

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The Examples which follow serve to illustrate this invention. The Examples are not intended to limit the scope of this invention, but are provided to show how to make and use the compounds of this invention.

201 Centigrade. Mass spectra were performed using fast atom bombardment (FAB) or electro-spray (ES) ionization. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

NMR were recorded at 250 MHz using a Bruker AM 250

spectrometer, unless otherwise indicated. Chemical shifts
are reported in ppm(δ) downfield from tetramethylsilane.

Multiplicities for NMR spectra are indicated as: s=singlet,
d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of
doublets, dt=doublet of triplets etc. and br indicates a

broad signal. J indicates the NMR coupling constant in

Hertz.

Celite® is filter aid composed of acid washed

inv all diatomaceous silica manufactured by Mansville Corp., Denver,

con 35. Colorado. Florisil® is an activated magnesium silicate

chromatographic support and is a registered trademark of

Floridon Co., Pittsburgh, Pennsylvania. Sat. indicates a

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saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant.

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Preparation of (2R:4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide hydrochloride). Seidergalinims

10 a) (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-

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Cbz-valinal (4.6 g, 1 eq) and glyoxal trimeric dihydrate (1.33 g, leq) were stirred in MeOH at -10°C. Ammonia was bubbled through the solution for several min and the mixture was allowed to stir for 4 h at -10°C. The mixture was allowed to warm to room temperature over 14 h, then was poured into 250 mL water. The suspension was filtered and the filter cake washed twice with water to give the title compound as a white solid (1.9 g, 36%). NMR(CD3OD) δ 7.28

20 (5H, m), 6.89 (2H, s), 5.04 (2H, dd), 4.46 (1H, d), 2.10 (1H, m), 0.91 (3H, d), 0.70 (3H, d); MS(CI/CH₄), m/e 274.2, [M+H]⁺, 230.1, 166.1, 123.1, 91.1.

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- b) (1'S)-1'-amino-1'-isopropyl-1'-(imidazo-2-yl)methane

 (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane (1.9 g) was stirred in methanol over 10% Pd/C (200 mg). Hydrogen was bubbled through the solution for 1 h and the solution was maintained under; a positive hydrogen atmosphere overnight. The mixture was filtered through

 Celite® and was evaporated to a tacky solid (720 mg; 75%).

 NMR (CDC13) & 6.87 (2H, s), 3.88 (1H, d), 2.04; (1H, m), 0.81 (6H, dd); MS (DCI/NH3) m/e 190.2 [M+H]*

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To a solution of (2R,4S,5S)-2-phenylmethyl-4-(t-butylmethyl) siloxy-5-(t-butoxycarbonyl) amino-6-phenyl-

hexanoic acid (200 mg, 0.38 mmol) in dichloromethane, (1'S)to: [- 1;-amino-1;-isopropyl-1'-(imidazo-2-yl)methane (48 mg, 0.35 polity commol), BOP reagent (168 mg, 0.38 mmol), and triethylamine The mixture was stirred (0.053 mL, 0.38 mmol); were added. The mixture was stirred . Notice 15 moundary argon overnight, and washed successively with water, 5% Remarks , reaqueous, sodium bicarbonate; and saturated aqueous sodium Ou. & & (a chloride. The solution was dried over MgSO4, filtered, and the solid was chromatographed (silica, 4% methanol/dichloromethane) to afford the title compound as a white solid (0.154 g, 68%). NMR(CDCl₃) δ 7.18 (10H, m), 6.91 (2H, d), 6.32 (1H, d), 4.69 (1H, d), 4.40 (1H, moon to t), 3.92 (1H, eq), 3.63 (1H, m), 2.84 - 2.31 (6H, m), 1.67 (4H, m), 1.24 (9H, s), 0.89 (9H, s), 0.74 (6H, dd), 0.05 (6H, here is a d); MS(DCI/NH3) m/e 649.6 [M+H]+. ... ₹ 8 50.5**15** 对抗 抗氯甲酚 **物质**多元 电流输出

butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(imidazo-2-yl)]methyl-hexanamide hydrochloride

The compound of Example 1(c) (0.140 g) was stirred in

20 THF at room temperature under an argon atmosphere.

Tetrabutyl ammonium fluoride (0.38 mL, 6 eq) was added and the solution was stirred overnight. The mixture was diluted with water and extracted with dichloromethane (3X). The combined organic extracts were washed with water and evaporated. The residue was treated with 1 eq of methanolic evaporated. The residue was treated with diethyl ether and extracted to give the title compound as a white solid (95 mg, 83%). NMR(DMSO-d6) & 7.78 (1H, d), 7.16 (10H, m), 6.71

(2H, s), 6.39 (1H, d), 4.68 (1H, m), 4.52 (1H, d), 2.71 (3H, d), 2.48 (3H, m), 1.97 (1H, m), 1.61 (1H, m), 1.30 (9H, s), 0.78 (3H, d), 0.61 (3H, d); MS(DCI/NH3) m/e 535.4 [M+H] + .

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uoi35 Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(tus os os butoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'-(4aminocarbonyl-thiazo-2-yl)]methyl-hexanamide

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a) Boc-valineamide

To a solution of di-t-butyl-dicarbonate (7:15 g, 1 eq) in dry dichloromethane was added valinamide hydrochloride (5.0 g, 1 eq) and triethylamine (9:14 mL, 2 eq). The mixture was heated to reflux for 4 h, and cooled to room temperature. The organic layer was washed twice with water and evaporated to give the title compound (6.03 g, 85%). NMR (CDCl3) δ 6.00 (1H, br), 5.54 (1H, br), 5.01 (1H, br), 3.93 (1H; dd), 2.12 (1H, m), 1.44 (9H, s), 0.92 (6H, dd)

a. b) Boc-valinethioamide (a. a. 16.3 (ar (01))

Boc-valineamide (0.5 g) was stirred in dry THF at room temperature under argon. Lawesson's reagent (1.56 g, 0.6 eq) was added and the mixture was stirred overnight. The solvent was evaporated and the residue chromatographed (silica, 2.5% methanol/dichloromethane) to give the title compound as a white solid (0.373 g, 70%). NMR(CDCl3) & 8.59 (1H, br s), 8.09 (1H, br s), 5.41 (1H, d (br)), 4.20 (1H, dd), 1.99 (1H, m), 1.39 (9H, s), 0.90 (6H, m).

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series (1'S)-1'-(t-butoxycarbonyl)amino-1'-isopropyl-1'-(4-

Boc-valinethioamide (0.265 g) was stirred in dry acetone under argon at -10°C. Ethylbromopyruvate (0.16 mL, 1.1 eq) 25 was added and stirred for 1 hat -10°C. The solution was poured into a well-stirred mixture of chloroform and water and then saturated with sodium bicarbonate. The organic phase was separated and the aqueous layer extracted with chloroform. The combined organic extracts were dried over 30 MgSO4, filtered, and evaporated to an oil; The oily residue was treated with trifluoroacetic anhydride (0.16 g) and pyridine (0.2 g) in dichloromethane for 1 h at -20°C. Excess solvent was removed in vacuo and the residue dissolved in dichloromethane. The solution was washed with sat. aqueous 35 sodium bicarbonate and 1.0N KHSO4 until pR 7. 1 The solution was dried over sodium sulfate, filtered, and evaporated to an oil which was chromatographed (silica, 4% methanol/ dichloromethane) to give the title compound as a tan solid.

1.53 .5. 25 NMR(CDCl₃): δ 8.04 (1H; as), 5.26 (1H; abrid), 4.85 (1H, m), 2 sw ap 4:37 (2H, q); 2.40 (1H, m), 1.41 (9H; s), 1.34 (3H, t), 0.93 (3H, d); 20.84 (3H, d). (3h) 2.5 (3H, d); 2.5 (3H, d); 3.6 (3H, d); 3.6 (3H, d). (3

5 d) (1'S)-1'-(t-butoxycarbonyl)amino-1'-isopropyl-1'-(4-

The compound of Example 2(c) (50 mg) was stirred in THF at 0°C. Excess 1.0N NaOH was added and the mixture was stirred for 12 h at 0°C. The mixture was diluted with 1.0N citric acid and extracted with dichloromethane (3X). The combined organic extracts were evaporated and dried in vacuo to give the title compound (0.045 g, 98%). NMR(CDCl3) & 8.08 (1H, s), 5.19 (1H, m), 4.80 (1H, m), 2.31 (1H, m), 1.38 (9H, s), 0.86 (6H, dd).

e) (1'S)-1'-(t-butoxycarbonyl)amino-1'-isopropyl-1'(4-aminocarbonylthiazo-2-yl)methane

(1'S)-1'-(t-butoxycarbonyl)amino-1'-isopropyl-1'-(4-

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(11.) (1.) (2R, 4S, 5S, 1°S) -2-phenylmethyl-4-(t-butyldimethylsiloxy) -5-35-(t-butoxy carbonyl) amino-6-phenyl-N-[1*-isopropyl-1*-(4-

'aminocarbonyl-thiazo-2-yl)]methyl-hexanamide

1.39 (9H, s), 1.39 (9H, s), 0.92 (6H, dd).

The compound of Example 2(e) (52 mg) was stirred in neat trifluoroacetic acid for 10 min and evaporated. The residue

(1H, "s(br), 6.28 (1H, s(br)), 5.24 (1H, d(br)), 4.82 (1H, m),

1.2.0

25

was diluted with methanol and treated with 2 eq of conc. HCl. The solvents were evaporated and dried (in vacuo; to give a white solid. This solid (40 mg) was added to a solution of (2R, 4S, 5S) -2-phenylmethyl-4-(t-butyldimethyl) siloxy-5-(tbutoxycarbonyl)amino-6-phenyl-hexanoic.acid2(97 mg, 1.1 eq), DCC (38 mg, 1.1 eq), and HOBT (0.05 g, 2.2 eq), in DMF at room The name temperature under argon. N-methylmorpholine (0.04 mL; 2.2 eq) was added and the mixture; was stirred overnight. The mixture was filtered through Celite®, evaporated, and diluted 10 with ethyl acetate. The solution was washed successively with 1.0N citric acid, 5% aqueous sodium bicarbonate, and to chromatographed (silica, 2.5% methanol/dichloromethane) to yield the title compound (60 mg, 55%). NMR(CDCl3) δ 7.89 (1H, s), 7.60 (1H, d), 7.24 (10H, m), 6.82 (1H, m), 5.12 (1H, m), 4.89 (1H, m), 3.92 (1H, q), 3.81 (1H, dd), 2.73 (4H, m), 2.21 (1H, m), 1.73 (2H, m), 1.40 (9H, s), 1.23 (1H, m), 0.93 (9H, s), 0.84 (6H, dd), 0.11 (6H, d), (2+1)

... refram(isr-i-osniddnxouren

g) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-) 20 butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(4one aminocarbonyl (thiazo-2-yl)]methyl-hexanamide

374, 356, 239.1, 202, 185.

The compound of Example 2(f) (60, mg) was stirred in dry Fifth the THF under argon and tetrabutylammonium fluoride (0.50 mL, 6 eq) was added. The solution was stirred at room temperature overnight. After diluting with water, the aqueous layer was million in (5. modile extracted with dichloromethane! (3X) = 5The combined organic extracts were washed with water, evaporated, and triturated with diethyl ether and ethyl acetate to give a tan solid. The solid was chromatographed (silica gel, 4% and the second methanol/dichloromethane) to give the title compound as a white solid (0.022 g). NMR(CDCl₃) δ 7.90 (1H, s), 7.15 (10H, m), 6.39 (1H, d), 5.93 (1H, br s), 5.06 (1H, dd), 4.91 (1H, d), 3.90 (1H, d), 3.67 (2H, m), 2.91 (4H, m), 2.64 (1H, d), 2.13(1H, m), 1.87 (3H, m), 1.36 (9H, s), 0.83 (6H, dd); $MS(DCI/NH_3)$ m/e 612 [M+NH₄]⁺, 595 [M+H]⁺, 495, 413.1, 391,

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mowed make the telegroup of the term terms. Example 3,
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Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-

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if reals (1'S)-1'-(t-butoxycarbonyl)amino-1'-isopropyl-1'-(thiazoia three 2-yl)methane organization and the real section

The compound of Example 2(c) was stirred in neat and the suspension was heated to 160°C for 2 h. After cooling to room

This cool systemperature, the solution was diluted with ethyl acetate and

combined and dried over MgSO4, filtered, and evaporated to a

15 (dark oil. The oil was chromatographed (silica, 4%

green and who was ablance for 10 bill. Though the Clarine

began with methanol/dichloromethane) storgive the title compound as an associationange oil. (2. NMR (CDCl3) $d\delta_0$ 7.68 (1H, ..d),:7.19 (1H, d), 5.26

3 (1H, d), 4.88 (1H, m), 2.31 (1H, m), 1.43 (9H, s), 0.92 (3H,

(4), (4) d), 10.84 (3H) d).) (p did) because (4.7)

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b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t
ansis a (butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(thiazo-2-

re temyl)]methyl-hexanamide to equation of temple and a

(and 180) (Discrept procedure of Example 2(f)-2(g), except oi 25 ogusing the compound of Example 3(a) in place of (1's)-1'-(t-10) but oxycarbonyl) amino-1'-isopropyl-1'-(4-aminocarbonylthiazo-deuc2-yl) methane, the title compound was prepared (88%).

31 NMR (DMSO-d6) 8 8.31, (1H, d), 7.62, (1H, d), 7.49 (1H, d), 7.16

-8 ((10H, m), 2.61 (6H, m), 1.28 (9H, s), 0.89 (3H, dd);

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degroile (tydigwyldigddio py telgoda) Example 401000 o garaf e

35 Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'-benzimidazo-

-i. n2-v1)1 methyl-hexanamide -- -- -- wantantantan

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a) (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(benzimidazo-2-yl)methane

Cbz-valine (2.0 g, 1 eq) was stirred at -10°C in dry THF under argon. Triethylamine (1.11 mL/1:0.eq) was added, followed by isobutyl chloroformate (1:03 ml, 1 eq). The reaction mixture was stirred for 10 min. Phenylene diamine control (0.944 g, 1.1 eq) was added slowly cin 10 mL dry THF. The mixture was warmed to room temperature and stirred for 1 h. The solvents were evaporated and the residue partitioned between water and ethyl acetate. The ethyl acetate layer was washed with 5% aqueous sodium bicarbonate and brine. The organic layer was dried over MgSO4, filtered, and evaporated. The residue was dissolved in glacial acetic acid and heated to 65°C for 16 h. The solvents were evaporated and the residue diluted with water. After neutralizing with my a saturated aqueous sodium bicarbonate, the solid was filtered and the filter cake was washed with hexane. The solid was $(k_{\rm c})$ recrystallized from ethyl acetate and hexane. NMR(CD3OD) δ 7.48-7.11 (9H, m), 5.06 (2H, q), 4.62 (1H, m), C2.27 (1H, m), 1.23 (1H, m), 1.02 (3H, d), 0.84 (3H, d).

b) (1'S)-1'-amino-1'-isopropyl-1'-(benzimidazo-2-yl) methane

The compound of Example 4(a) (2.76'g) was stirred in

methanol. 10% palladium on activated carbon (Pd/C) (250 mg)

25 was added and hydrogen gas was bubbled through the solution

for 1 h. The reaction was maintained under an hydrogen

atmosphere overnight. The mixture was filtered through

Celite® and the solvents evaporated to give the title

compound as a white solid (1.58 g, 98%). NMR(CDCl3) & 7.48
30 7.10 (4H, m), 4.02 (1H, d), 2.24 (1H, m), 0.96 (3H, d);

dyn of a no 2- (8, 1,53, 3 3)

c) (2R,4S,5S,1'S)-2-phenylmethyl-4-(t-butyldimethyl)siloxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'35 benzimidazo-2-yl]methyl-hexanamide 11 32 Rais 25

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To a solution of (2R, 4S, 5S)-2-phenylmethyl-4-(t-butyldimethyl)siloxy-5-(t-butoxycarbonyl)amino-6-phenyl-hexanoic acid (75 mg, 1.1 eq) in dimethyl formamide under

. 0.83 (3H, d); MS(DCI/NH3) m/e 190.2 [M+H] tar 10 04 9

- argon, the compound of Example 4(b) (25 mg, 1.0 eq), DCC (30 mg, 1.1 eq) and HOBT (44 mg, 2.2 eq) were added. The mixture was stirred overnight, then filtered through Celite®. The solvents were evaporated and the residue was
- 5 chromatographed (silica gel, 4% methanol/dichloromethane) to give the title compound (0.070 g, 78%). NMR(CDCl₃) δ 7.88 (1H, d), 7.30 (14H, m), 6.80. (1H, d), 4.93 (2H, m), 4.26 (1H, q), 4.00 (1H, m), 2.92 (7H, m), 2.01 (2H, m), 1.53 (9H, s), 1.20 (9H, s), 1.14 (6H, d), 0.41 (6H, d); MS(DCI/NH₃) m/e 10 699.6 [M+H]⁺.
- (EMAN) (2R,4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'-benzimidazo-2-yl]methyl-hexanamide
- The compound of Example 4(c) was stirred in dry THF and tetrabutyl ammonium flouride (0.6 mL, 6 eq) was added. The mixture was stirred under argon overnight at room temperature. The solution was diluted with water and extracted with dichloromethane (3X). The combined organic layers were washed with water and evaporated to a residue which was chromatographed (silica, 2% methanol/CH₂CL₂) to give the title compound (0.029 g, 50%). NMR(CDCl₃) & 7.54 (1H, m), 7.11 (11H, m), 6.69 (4H, s), 4.98 (1H, d), 4.69 (2H, m), 3.66 (2H, m), 2.74 (5H, m), 2.31 (1H, m), 1.73 (2H, m), 1.32 (9H, s), 0.70 (6H, d); MS(DCI/NH₃) m/e 585.4 [M+H]⁺, 413.3, 364.3, 296.2, 190.2, 173.1, 120.1.

Example 5

30 Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-(1'-imidazo-2-yl)methyl-hexanamide hydrochloride

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a) 2-(carbobenzyloxyamino) methyl-imidazole

(6.35:01) Following the procedure of Example 1(a), except
substituting Cbz-glycinal for Cbz-valinal, the title compound
was prepared. NMR(CDCl3) 8.33 (5H, s), 6.95 (2H, s), 5.95

10

20

(1H, s(br)), 5.12 (2H, s), 4.42 (2H, d); MS(DCI/NH3) m/e
232.2 [M+H]+, 188, 171.

b) (2R,4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(t-'5 butoxycarbonyl)amino-6-phenyl-N-(1'-imidazo-2-yl) methyl-hexanamide hydrochloride

Following the procedure of Example 1(b)-1(d), except substituting the compound of Example 5(a) for (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane, the title compound was prepared. NMR(CD3OD) & 7.20 (10H,m), 6.94 (2H,s), 6.11 (1H,d), 4.24 (2H,dd), 3.61 (1H,m), 3.52 (1H,m), 2.69 (4H,m), 1.66 (2H,m), 1.28 (9H,s); MS (DCI/NH3) m/e 493.7 [M+H]+, 475.7, 120.2, 98.2, 83.1, 69.1

Example 6" The state of the sta

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a) (1'S)-1'-carbobenzyloxyamino-1'-methyl-1'-(imidazo-2-yl)methane

Following the procedure of Example 1(a); except substituting Cbz-alanal for Cbz-valinal; the title compound was prepared. NMR(CDCl₃) δ .35 (5H,s), 6.92 (2H,s); 5.52(1H,d), 5.12 (2H,q), 4.90 (1H,q); MS(DCI/NH₃) m/e 246 [M+H]+, 202, 185.

b) (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-[1'-methyl-1'-(imidazo-2-yl)] methyl-hexanamide hydrochloride

Following the procedure of Example 1(b)-1(d), except substituting the compound of Example 6(a) for (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane, the title compound was prepared. NMR(CD3OD) 8 7.11(10H; m), 6.86 (2H, s), 4.69 (1H, d), 3.62 (1H, d), 3.51 (1H, m), 2.68 (6H, m), 1.59 (2H, m), 1.30 (9H, s), 1.14 (3H, d); MS(DCI/NH3) m/e 507.5 [M+H]+, 489.4, 112.1.

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a) (1'S)-1'-carbobenzyloxyamino-1'-benzyl-1'-(imidazo-2-yl)methane

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10 Following the procedure of Example 1(a), except

""" substituting Cbz-phenylalaninal for Cbz-valinal, the title

compound was prepared. NMR(CDCl₃) δ 7.37-7.05 (10H,m), .6.95

(2H, s br), 5.52 (1H, d), 5.05 (2M, s), 4.95 (1H, q), 3.32

(2H, d); MS(DCI/NH₃) m/e 322, 261, 171.

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b) (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(t-s)
butoxycarbonyl)amino-6-phenyl-N-(1'-benzyl-1'-(imidazo-2-yl))
methyl-hexanamide hydrochloride

and did Following the procedure of Example 1(a)-1(d), except

20 substituting the compound of Example 7(a) for (1'S)-1'
carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane,
the title compound was prepared. NMR(CD3OD) & 7.15 (15H, m),

1 2 6 6 7 9 (2H, S), 5 7 8 (1H, d), 5 04 (1H, d), 3 5 8 (1H, m), 3 . 47

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ShiverPreparation of (2R.4S.5S.1'S)-5-(carbobenzyloxy)amino-4-ShiverPreparation of (2R.4S.1'S)-5-(carbobenzyloxy)amino-4-ShiverPreparation of (2R.4S.1'S)-5-(carbobenzyloxy)amino-4-ShiverPreparation of (2R.4S.1'S)-5-(carbobenzyloxy)amino-4-ShiverPreparation of (2R.4S.1'S)-5-(carbobenzyloxy)amino-4-ShiverPreparation of (2R.4S.1'S)-5-(carbobenzyloxy)amino-4-ShiverPrepara

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A solution of (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino2004-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide:(0.086.g) in trifluoroacetic acid was
35 stirred for:10 min, then was evaporated in vacuo. To the

[6) i ac cresidue were added dimethylformamide, benzylchloroformate (1
3 eq) and triethylamine:(5 eq), and the resulting mixture was
stirred at room temperature for 16 h. The reaction mixture

was poured into H₂O and extracted with dichloromethane. The combined organic extracts were evaporated, and the residue was triturated with diethyl ether to afford the title compound as a white solid. NMR(CD3OD):017.36-6494 (15H, m), 5:6.84 (2H, s), 4.99 (2H, s), 4.54 (2H, d):043.763 (1H, m), 3.52 (1H, dd), 2.77 (5H, m), 2.043 (1H, m), 21.763 (1H, m), 1.58 (1H, m), 0.82 (3H, d), 0.66 (3H, d).

Example 9 Challenn(Ly

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Preparation of (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4,5-dimethyl)imidazol-2yllmethyl-6-phenyl-2-phenylmethyl-hexanamide (2013)

3) (188)-11-caubing/abyanghabas-14-(810) (6

indiam ag the procedure of a ministra

a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4,5-dimethylimidazol-2-yl)methane

Cbz-Valinal (4.14 g) was stirred in methanol with 2,3-butanedione (1.54 mL, 1.0 eq). Ammonia was bubbled through the solution at -25°C for 5 min. The cooling bath was

- removed and the mixture allowed to warm to 20°C and The solution was stirred for 16 h under Ar. The solvents were removed by rotary evaporation, and the residue was diluted with dichloromethane and extracted with dilute aqueous HCl. The organic layer was concentrated to afford unreacted Cbz-
- valinal (4.02 g). The acidic aqueous layer was basified with 1N NaOH and extracted with dichloromethane, the organic extract was concentrated and the residue purified by flash chromatography (4% methanol in dichloromethane) to provide the title compound as a white solid (50 mg). NMR (CD₃OD) δ
 - 7.29 (5H, m), 5.04 (2H, dd), 4.38% (1H, d) y 2.06% (6H; s) 2.01 (1H, m), 0.93 (3H, d), 0.77 (3H, d).

mained by the larger from () -d-spring at 70 (82) Communication (6)

- -(-fylacub) (1S)-1-(4,5-dimethylimidazol-2-yl)-2-methylpropylamine
- hydrogenolysis using the same procedure as described of previously in Example 1(b) concept using the product of 1(a) (50 mg), to afford the title compound as a white solid

and the state of the state of the

- 2.06 (6H, s), 2.00 (1H, m), 0.71 (6H, dd).
 - c) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-t
 butyldimethylsiloxy-N-[1'-isopropyl-1'-(4,5-dimethyl)

 imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

Using the procedure of Example 1(c), except substituting (2R,4S,5S)-5-(t-butoxycarbonyl)amino-4-t-butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid and (1S)-1-(4,5-

dimethylimidazol-2-yl)-2-methylpropylamine (24 mg), the title compound was prepared (55 mg, 57%). NMR(CDCl3) & 7.26-6.80

(10H, m), 4.65 (1H, d), 4.24 (1H, dd), 3.87 (1H, q), 3.61 (1H, m), 2.77-2.39 (5H, m), 2.22 (1H, m), 1.98 (6H, s), 1.79

13.5 (1H, m), 1.58 (1H, m), 1.24 (9H, s), 0.85 (9H, s), 0.69 (6H,

- d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4, 5-dimethyl) imidazol-2-yl] methyl-6-phenyl-2-phenylmethyl-hexanamide
- By following the deprotection procedure described in Example 1(d), except using (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4,5-dimethyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide (55 mg) and omitting the final
- 25 treatment with methanolic HCl, the title compound was prepared (25 mg, 62%). NMR(CDCl3) & 7.29-6.88 (10H, m), 4.98 (1H, br d), 4.47 (1H, m), 4.29 (1H, m), 3.58 (2H, m), 2.84-2.51 (5H, m), 2.20 (1H, m), 2.04 (6H, s), 1.71 (2H, m), 1.38

(9H, s), 0.69 (6H, dd).

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Example 10

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl) amino-4hydroxy-N-[1'-isopropyl-1'-(4.5-dimethyl) imidazol-2-

35 <u>yllmethyl-6-phenyl-2-phenylmethyl-hexanamide</u>

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a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4-phenylimidazol-2-yl)methane

Using the procedure of Example 1(a), except using Cbz-(L)-valine (2.19 g) and α-ketophenylacetaldehyde instead of glyoxal, the title compound was prepared (1.54 g, 48%). NMR(CDCl₃) δ 7.62 (1H, (br)), 7.24 (10H, m), 5.79 (1H, d), 5 5.04 (2H, dd), 4.32 (1H, dd), 2.31 (1H, m), 0.96 (3H, d), 0.79 (3H, d); MS m/e 350.4 [M+H]⁺, 199.0.

b) (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-[1'-isopropyl-1'-(4-phenyl) imidazol-2yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

Using the procedure of Example 1(b)-1(c), except using the compound of 10(a) (72 mg), the title compound was prepared (67 mg, 44%). NMR(CDCl₃) & 7.70 (1H, d), 7.40-6.71 (16H, m), 4.73 (1H, d), 4.54 (1H, dd), 3.96 (1H, q), 3.69 (1H, m), 2.88-2.36 (5H, m), 1.73 (2H, m), 1.33 (9H, s), 0.91 (9H, s), 0.84 (6H, dd), 0.11 (6H, d); MS m/e 725.4 [M+H]+.

c) (2R, 4s, 5s, 1's)-5-(t-butoxycarbonyl)amino-4-hydroxy-N[1'-isopropyl-1'-(4-phenyl)imidazol-2-yl]methyl-6-phenyl-2phenylmethyl-hexanamide

Using the procedure of Example 9(d), except starting from (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-phenyl) imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide (67, mg), the title compound was prepared (30 mg, 54%). NMR(CDCl3) & 7.52-6.67 (16H, m), 5.48 (1H, d), 3.60 (1H, q), 3.44 (1H, d), 2.60 (4H, m), 1.96 (1H, m), 1.62 (2H, m), 1.23 (9H, s), 0.73 (3H, d), 0.62 (3H, d); MS m/e 611.4 [M+H]⁺, 242.2, 195.0, 150.2.

Example 11

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(N'-methyl)imidazol-2-yllmethyl-6phenyl-2-phenylmethyl-hexanamide

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a) (1S)-carbobenzyloxyamino-l-isopropyl-l-(N'-methylimidazol-2-yl)methane
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at 40°C for 2 h in methyl iodide (5 mL). The reaction

- 5 mixture was evaporated, and the residue was suspended in aqueous Na₂CO₃. The mixture was extracted with
- product was purified by flash chromatography (silica, 2% methanol/dichloromethane) to yield the title compound (200
 - 10 mg, 70%). NMR (CDCl₃) δ 7.29 (5H, s), 6.92 (1H, s), 6.69 (1H, s), 5.94 (1H, d), 5.03 (2H, q), 4.55 (1H, dd), 3.64 (3H, s),

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1 MARS the 2.20 (1H, m), 1.01 (3H, d), 0.82 (3H, d). 10 (Web Ar

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- ac & b): (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-.:
- , (pp 15 butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-methyl)imidazol-2-
- rot protylemethyl-6-phenyl-2-phenylmethyl-hexanamide are pro-
- using the compound of 11(a) (90 mg), the title compound was prepared (104 mg, 50%), NMR(CDCl3) & 7.32-6.89 (10H, m),
- bxo1020 0 6.81 (1H, s), 6.59 (1H, s), 6.08 (1H, d), 4.71 (2H, m), 3.94 (1H, g), 3.70 (1H, m), 3.25 (3H, s), 2.80-2.36 (5H, m), 2.21 (7.3 (2H, m), 1.73 (2H, m), 1.31 (9H, s), 0.94 (9H, s), 0.85 (6H,
 - dd), 0.11 (6H, s).
 - 25:dec) (2R, 4S, 5S, 1.S) -5= (t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1!=:(N'=methyl) imidazol-2-yl]methyl-6-phenyl-2-yphenylmethyl-hexanamide (48) base and 3 directors.
- mon1 (055% diffollowing the procedure of Example 9(d), Dexcept using (501) 01(2R,4S 5S,1!S)-5-(t-butoxyce-bonyl)amino-4-t-05-3888
 - (30 % butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-methyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide (100 mg), the title compound was prepared (74 mg, 89%). NMR(CDCl₃) δ 7.21-6.74 (11H, m), 6.70 (1H, s), 6.59 (1H, s), 4.95 (1H, d), 4.61 (1H, dd), 3.60 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (1H, dd), 3.60 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (1H, dd), 3.60 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (1H, dd), 3.60 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (1H, dd), 3.60 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (1H, dd), 3.60 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (1H, dd), 3.60 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (3H, m), 3.48 (3H, s), 3.48 (3H, s
 - 35 m), 1.64 (2H_{ext}m), 1.32 (9H_{ext}s), 0.82 (3H, d), 0.63 (3H, d);

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Example 12 add to the 19 () some

Preparation of (2R,4S,5S,1'S)-5-(t-butoxycarbonvl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-vl)methyl-6-phenyl-2-(3-phenylpropargyl)hexanamide be so gave gow especies

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a) (3R,5S,1'S) - (1'-t-butoxycarbonylamino-2'-phenyl) ethyl-3-(3-phenylpropargyl)-tetrahydrofuran-2-one se decisary

To a solution of lithium diisopropylamide (3761 mL, 2.0 M in THF, 2.2 eq) in THF at -78°C under an argon atmosphere, (5S,1'S)-(1'-t-butoxycarbonylamino-2'-2 phenyl) ethyl-tetrahydrofuran-2-one (1.0 /g, 1.0 eq) was added. After stirring at -78°C for 15 min, hexamethylphosphoramide (1.14 mL, 2 eq) was added, and stirring was continued an -10.15 additional 10 min. Phenylpropargyl bromide (1.28 g, 2.0 eq), was added and the resulting mixture was stirred at -78°C for 2 h, then poured into dilute aqueous HCl and extracted with dichloromethane. The combined organic extracts were evaporated under reduced pressure to an oil, which was chromatographed (silica, 20% ethyl acetate/hexanes) to afford the title compound as a white solid (0.455 g, 33%) (100, 100) NMR (CDC13) δ 7.18 ((10H, m), 4.50 (2H, m)), 3.93 (1H, q), 2.79 (5H, m), 2.23 (2H, m), 1.24 (9H, s). (B), 11.7 (E)

> b) (2R, 4S, 5S)-5-(t-butoxycarbonyl)amino-4-t-butyldimethylsiloxy-6-phenyl-2-(3-phenylpropargyl) hexanoic acid

The title compound (496 mg, 84%) was prepared by the procedure of Evans et al., J. Org. Chem: 50;14615 (1985) from

m), 4.71 (1H, d), 3.94 (3H, m), 2.69 (4H, m), 1.590 (2H, m), 1.31 (9H, s), 0.89 (9H, s), 0.11 (6H, d); 3-4 vinter 1/2

c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-(1'-isopropyl-i'-imidazol-2-yl)methyl-6-phenyl-2-(3-phenylpropargyl) hexanamide (1) (1) (1)

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Following the procedure of Example 1(c), except using (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-6-phenyl-2-(3-phenylpropargyl) hexanoic acid (240 mg) and

(1S)-1-imidazol-2-yl-2-methylpropylamine, the title compound was prepared (244 mg, 84%). NMR(CDCl₃) & 7.14 (12H, m), 6.72 (1H, d), 4.58 (1H, d), 4.49 (1H, dd), 3.92 (1H, q), 3.80 (1H, m), 2.54 (5H, m), 1.65 (2H, m), 1.20 (9H, s), 0.81 (9H, s), 0.85 (0.80 (6H, dd), 0.05 (6H, d).

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or aldress a collection was take that

- d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-(3-yphenylpropargyl) hexanamide
 - 10 :: Following the procedure of Example 9(d), except using (2R, 4S, 5S, 1'S) = 5 (t-butoxycarbonyl) amino-4-t-

Description of Example 13 to give the company of

503.2, 485.2, 459.2, 441.2.

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(: Preparation of (2R.4S.5S.1'S)-5-(isopropoxycarbonyl) amino-4
hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2
phenylmethyl-hexanamide

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- 25 meaning to the secretary from the last of the last
- isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
- pullit hexanamide behilf super adults of the levels are set to the behilf are restricted by the product of Example 1(c) (0.20 g, 0.31 mmol) was
- ### 1980 (#dissolved in strifluoroacetic acid and stirred at room of the first string of the string
- dichloromethane and saturated aqueous Na₂CO₃. The organic
- and the extract was dried over Na₂CO₃, filtered and evaporated to
- 35 (without further purification. 1998) Which was used
 - b) (2R, 4S, 5S, 1'S) -5-(isopropoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-

isopropoxycarbonyl) imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

A mixture containing the compound of 13(a) (0.17 g, 0.31 mmol), isopropyl chloroformate (0.62 mL, 1M in

- eq) in dichloromethane (40 mL) was allowed to stir at room temperature overnight under an argon atmosphere. The mixture was then partitioned between dichloromethane and saturated aqueous Na₂CO₃, and the organic extract was dried over Na₂CO₃.
- The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 4%.6) methanol/dichloromethane) to afford the title compound (0.214 g, 96%). NMR(CDCl₃) δ(7.35-6.78 (12H, m), 6.57 (1H, d), 5.61 (1H, dd), 5.19 (1H, m), 4.86 (1H, m), 4.77 (1H, d), 3.97 (1H, d), 3.63 (1H, t), 2.88 (1H, dd), 2.70-2.48 (4H, m), 2.06 (1H, m), 2.00-1.85 (1H, m), 1.79-1.64 (1H, m), 1.45 (6H, dd), 0.94 (9H, s), 0.85 (6H, d), 2.12 (6H, d), 3.33 (22)
 - c) (2R,4S,5S,1'S)-5-(isopropoxycarbonyl)amino-4-hydroxy-N(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

methanol, excess aqueous HCli(-5 eq) was added. The resulting solution was allowed to stir at room temperature

- overnight, and was concentrated under reduced pressure. The residue was diluted with H2O, and basified with aqueous Na₂CO₃. The mixture was extracted with dichloromethane, and the combined organic extracts were dried over Na₂CO₃. The solvent was removed (in vacuo, and the residue was purified by
 - flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (0.150 g; 97%) σπΝΜΚ (CDCl3) δ 7.32-

4.87 (1H, m), 3.78 (1H, m), 3.62 (1H, m), 3.25 (1H, m), 2.96-2.67 (4H, m), 2.29 (1H, m), 1/95-1.65 (2H, m), 1.25-1.12 (6H,

35 dd), 0.80-0.60 (6H, dd); MS m/e 521 [M+H]+, 519 (M-H) - 38

5 (5) (3 **9** 44 (3 12**6**5 (3 12**3**5)

2 (isopropoxycarbonyl) amino-4-hydroxy-N-. Section (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

ex-Conteque:phenylmethyl-hexanamide:hydrochloride:ediplotationale

the second sufficient product of (13'(c) (100 mg, 0.192 mmol) was dissolved O(5 \in) methanol (10 mL) and a 1M solution of HCl in ether (0.192 more les mL) was added. as The solution was concentrated by rotary

for 15 of evaporation without heating; and the residue was trituated

os (with ether and dried under vacuum to afford the title.

33.7% (compound (104 mg, 98%). NMR(CD₃OD) δ 7.30 (2H, s), 7.21-

10 (6.88(10H, m), 4.61%(2H, m), 3.65 (1H, m), 3.48 (1H, d), 2.99

ANS: VELA (1H, m), 2.87 (1H, m), 2.74-2.56 (2H, m), 2.12 (1H, m), 1.75-

(h (1) 1.50 (2H, m), 1.17-1.00 (6H, dd), 0.90 (3H, d), 0.64 (3H, d).

Example 14

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Preparation of (2R.4S.5S.1'S)-5-(benzyloxyethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenvl-2-phenvlmethyl-hexanamide

- 20 a) benzyloxyethyl-(4-nitro)phenylcarbonate
- To Ca solution of 2-benzyloxyethanol (2.5 g, 16.4 mmol)
- $^{2.18}$ $^{18.13}$ and bis(4-nitrophenyl)carbonate (5.0 g, 1 eq) in

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- " . . . dichloromethane (200 mL), N-methylmorpholine (1.81 mL, 1 eq) was added. The resulting mixture was allowed to stir at room
 - temperature for 3 d. The reaction mixture was washed successively with H20 and saturated aqueous NaCl and dried over Na₂SO₄. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 20%
 - methyl acetate/hexanes) to afford the title compound (4.38 g, 30 84%). NMR (CDCl₃) δ 8.26 (2H, m), 7.34 (7H, m), 4.62 (2H, s),
 - 4.49 (2H, t), 3.70 (2H, t).
- b) (2R, 4S, 5S, 1'S) -5- (benzyloxyethoxycarbonyl) amino-4-t--igh. Smig butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-benzyloxyethoxy-

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- 35 carbonyl)imidazol-2-yllmethyl-6-phenyl-2-phenylmethyl-6 priso othexanamidel cognoxi to program as a solweither.
 - -1) Tota solution of the compound of Example 14(a) (134.5
 - mg, 0.24 mmol) in dichloromethane (40 mL) under an argon

atmosphere, benzyloxyethyl 4-nitrophenyl carbonate (160 mg, 2 eq) and 4-dimethylaminopyridine (60 mg/20 eq) were added. The resulting mixture was allowed to stir at room temperature overnight, and wasadiluted with dichloromethane. The organic extract was washed successively with aqueous Na₂CO₃, H₂O, aqueous Na₂CO₃ and H₂O, and dried over Na₂CO₃ ... The solvent be the . was removed in vacuo, and the residue was purified by flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (180 mg, 82%). NMR (CDCl₃) δ 7.45-10 .6.80 (22H, m), 6.62 (1H, d), 5.60 (1H, t), 5.06 (1H, d), 4.60 (2H, s), 4.52 (2H, s), 4.50 (2H, m), 4.31 (1H, m), 4.07 (2H, (i) (iii) (iii), 3.80 (2H, it), 3.68 (1H, q), 3.57 (1H, q), 2.85 (1H, m), 2.77-2.41 (4H, m), 2.09 (1H, m), 1.90 (1H, m), 1.73 (1H, m), 0.95 (9H, s), 0.81 (6H, dd), 0.11 (6H, d).

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c) (2R,4S,5S,1'S)-5-(benzyloxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

Following the procedure of Example 13(c), except using the compound of Example 14(b) +(160 mg), the title (compound 20 was prepared (100 mg, [81%). NMR(CDCl₃, CD₃OD) δ 7.40-6.79 (17H, m), 4.55 (2H, s), 4.45 (1H, d), 4.20 (2H, m), 3.80-3.45 (5H, m), 2.95-2.66 (4H, m), 2.590(1H, dd), 2.07 (1H, m), 1.71 __(2H_e:m), 0.80 (3H_e:d), 0.68 (3H_e:d).alid - webbin use:

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Preparation of (2R.4S.5S.1'S)-5-(methoxycarbonyl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2

a) (2R, 4S, 5S, 1'S) -5-(methoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-[1!-isopropyl-1!-(N'-), N. . (4) methoxycarbonyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-35 hexanamide and Ly-1-10 shim (Ly-1-10 shim)

Following the procedure of Example 13(b) except using (2R, 4S, 5S, 1'S) -5-amino-4-t-butyldimethylsiloxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-

- hexanamide, the title compound was prepared (89%).

 NMR(CDCl₃) & 7.40-6.79 (12H, m), 6.52 (1H, d), 5.58 (1H, dd),

 4.91 (1H, d), 3.96 (3H, s), 3.95 (1H, d), 3.66 (1H, t), 3.60

 (3H, s), 2.85 (1H, m), 2.73-2.40 (4H, m), 2.08 (1H, m), 1.90

 5 (1H, m), 1.69 (1H, m), 0.95 (9H, s), 0.85 (6H, dd), 0.14 (6H, d).
 - b) (2R,4S,5S,1'S)-5-(methoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 13(c), except using the compound of Example 15(a), the title compound was prepared (70%). NMR(CDCl₃, CD₃OD) δ 7.23-6.60 (12H, m), 4.38 (1H, d), 3.65 (1H, t), 3.54 (3H, s), 3.33 (1H, m), 2.95 (1H, 15 m), 2.82-2.40 (4H, m), 1.95 (1H, m), 1.64 (2H, m), 0.69 (6H, dd).

Example 16

- 20 Preparation of (2R.4S.5S.1'S)-5-(ethoxycarbonyl)amino-4
 (a hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-bexanamide
 - a) (2R, 4S, 5S, 1'S) 5 (ethoxycarbonyl) amino 4 t -
 - 25 butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-

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- Willer ethoxycarbonyl) imidazol-2-yl]methyl-6-phenyl-2-phenylmethyllhexanamide of () the graph of the state of the st
- procedure of Example 13(b), except using a (2R,4S,5S,1'S)=5-amino-4-t-butyldimethylsiloxy=N-(1'-
- 30 1 isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
- (MI) 63. Shexanamide and ethylchloroformate, the title compound was (80) 82 (prepared (90%). NMR(CDCl3) & 7.35-6.77 (12H, m), 6.55 (1H,
 - d), 5.60 (1H, dd), 4.86 (1H, d), 4.41 (2H, m), 4.15-3.90 (3H,
 - m), 3.66 (1H, t), 2.87 (1H, m), 2.75-2.45 (4H, m), 2.08 (1H,
 - 35 m), 1.92 (1H, m), 1.70 (1H, m), 1.45 (3H, t), 1.18 (3H, t), 0.98 (9H, s), 0.85 (6H, dd), 0.13 (6H, d).

b) (2R, 4S, 5S, 1'S) -5-(ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 13(c), except using the compound of Example 16(a), the title compound was prepared (95%). NMR(CDCl₃, CD₃OD) δ 7.25-6.75 (12H, m), 4.43 (1H, d), 3.95 (2H, q), 3.61 (1H, q), 3.40 (1H, m), 2.85 (1H, m), 2.80-2.40 (4H, m), 2.05 (1H, m), 1.61 (2H, t), 1.11 (3H, t), 0.72 (3H, d), 0.55 (3H, t).

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-vl)methyl-6-phenyl-2-(3-phenyl-2-propenyl)hexanamide (1) 01 3-18.

a) (3R,5S,1'S)-(1'-t-butoxycarbonylamino-2'-phenyl)ethyl-3-(3-phenylprop-2-enyl)-tetrahydrofuran-2-one

Following the procedure of Example 12(a), except using cinnamyl bromide (0.485 mL) as the alkylating agent, the title compound was prepared (0.51.g, 75%). NMR (CDCl₃) δ 7.35-7.10 (10H, m), 6.43 (1H, d), 6.09 (1H, m), 4.60 (1H, m), 4.48 (1H, q), 4.00 (1H, t (br)), 2.96-2.55 (4H, m), 2.53-2.21 (2H, m), 2.05 (1H, m), 1.35 (9H, s).

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b) (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethyl-siloxy-6-phenyl-2-(3-phenyl-2-propenyl) hexanoic acid

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Following the procedure of Example 12(b), except using the compound of Example 17(a), the title compound was prepared (77%). NMR(CDCl₃) & 7.40-7.05 (10H, m), 6.48-6.00 (4H, m), 4.78 (1H, d), 3.94 (1H, q), 3.80 (1H, m), 2.89 (1H, m), 2.83-2.26 (4H, m), 1.90 (1H, m), 1.59 (1H, m), 1.28 (9H, s), 0.90 (9H, s), 0.08 (6H, d).

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butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2-propenyl)hexanamide
```

Following the procedure of Example 1(c), except using 5 to the compound of, 17(b), the title compound was prepared (82%).

NMR (CDCl₃); δ 7.35-7.15 (10H, m), 7.14-6.85 (2H, m), 6.73 (1H,

ban dads t), 3.97 (1H, q), 43.76 (1H, m), 2.77 (2H, d), 2.50-2.25 (2H,

Hq = 3 m), 2.12 (1H, m), 61.70 (1H, m), 1.63 (1H, m), 1.36 (9H, s), 10 0.92 (9H, s), 0.81 (6H, d), 0.09 (6H, d). 5 5 5 5 5 5

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d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2is) 07.5 propenyl)hexanamide (60.) 5-3 (1.0.85) (27.0.5)

15.31) Following)the procedure of Example 9(d), except using the compound of 17(c), the title compound was prepared (90%).

NMR(CDCl₃, CD₃OD) & 7.30-7.00 (10H, m), 6.71 (2H, s), 6.26

(1H, d), 6.41 (1H, m), 3.66 (1H, d), 3.50 (1H, d), 2.88-2.45

(4H, m), 2.36 (1H, m), 2.23 (1H, m), 2.06 (1H, m), 1.70 (2H,

20 m), 1.34 (9H, s), 0.88 (3H, d), 0.74 (3H, Fid) Fit (3H, Fid) (9H, s) to the fide of the second se

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Language of 30 and the second parameters of the third compound than the control of 30 and 30 and the second through the control of 30 and 30 a

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4
6 , % hydroxy-N-[1'-isopropyl-1'-(4-nitroimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide

(1, 10) NMR (CD₃OD) δ 6.95 (2H, s), 4.72 (1H, d, J=6 Hz), 2.35-2.10

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- b) (1S)-N-(1-(4-nitroimidazol-2-yl)-2-methyl) propylacetamide

 The compound of Example 18(a) (290 mg;q:1:60 mmol) was

 dissolved in cold concentrated H₂SO₄ (2 mL) ; and after

 stirring for 15 min, 90% HNO₃ (0:4 mL) was added dropwise.
- The resulting mixture was slowly warmed to 40°C and stirred for 2 h. The mixture was then poured onto ice; and the pH
- was adjusted to 4 by the addition of solid NaHCO3. The mixture was extracted with ethyl acetate (6x), and the combined organic extracts were dried over MgSO4 and concentrated under reduced pressure to afford the title
- compound (153 mg, 42%). NMR(CD3OD) 5.7.98; (1H, s), 4.70 (1H, 15 d, J=6 Hz), 2.35-2.15 (1H, m), 1.98; (3H, s), 0.95 (3H, d, J=5 Hz); MS m/e 475.2 (2M+Na)+, 0.249.2

(M+Na)+, 227.2 [M+H]+, 185.2; 168.0.00600 (ELOC) HM

- dr S. do Joyan (180-1-(4-nitroimidazol-2-yl), 2-methylpropylamine,
 - 20 dihydrochloride salt (n. (E.) HB.O. (H. (E.) FE.F. (H.

A mixture of the compound of Example 18(b) 6(153 mg, 0.68 mmol) in 6N HCl (2 mL) was heated at 90°C for 12 h, cooled and concentrated under reduced pressure. The title compound was obtained (138 mg, 80%) and used without further purification. NMR(CD3OD) 8 8.12 (1H; s), 4.30 (1H; d, J=4

Hz), 2.45-2.30 (1H, m), 1.12 (3H, 1d, 5)=4(Hz); 0.90%(3H, d, J=4 Hz).

- d) (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-t- (1)
- butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-nitroimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide(6)

Following the procedure of Example 1(c), except using (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid and (1S)-1-(4-3)

- nitroimidazol-2-yl)-2-methylpropylamine, the title compound was prepared. NMR(CDCl₃), 8,7.30-6.90, (10, H_{r,j,m}), 6.60 (1H, d, J=4 Hz), 4.70 (1H, d, J=5 Hz), 4.40 (1H, t, J=4 Hz), 3.90
 - 11 Sec (1H, q, J=4 Hz), 3.75 (1H, dd, J=8, 3 Hz), 2275-2.30 (6H, m),

1.80-1.50 (2H, m), 1.25 (9H, s), 0.85 (9H, s), 0.70 (6H, m), 0.05 (6H, d) J=4 Hz).

The second of the the tenton of the first of the second

- Following the deprotection procedure of Example 1(d),
 except using (the compound of Example 18(d), the title
 compound was prepared. NMR(CD3OD) δ 7.90 (1H, s), 7.40-6.90
- (10H, m), 4.53 (1H, d, J=6 Hz), 3.70 (1H, m), 3.50 (1H, m), 2.90-2.60 (5H, m), 2.00 (1H, m), 1.90-1.55 (2H, m), 1.49 (9H, s), 0.85 (3H, d, J=4 Hz), 0.70 (d, 3H, J=4 Hz); MS m/e 602.4 (M+Na)+, 580.4 [M+H]+, 524.4, 480.4.

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Example 19

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-(1'-ethyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

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a) (1S)-1-carbobenzyloxyamino-1-ethyl-1-(imidazol-2-yl)methane

Following the procedure of Example 1(a), except using Cbz-(L)-α-ethylglycinal in place of valinal, the title compound was prepared. NMR(CDCl₃) δ 7.45-7.10 (5H, m), 6.90 (2H, ms), 5.65 (1H, d, J=6 Hz), 5.10-4.95 (2H, m), 4.40 (1H, q, J=5 Hz), 2.00-1.70 (2H, m), 1.00-0.80 (3H, m).

in the base b) (1S) - (1-imidazol-2-yl) propylamine

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30 Following the procedure of Example 1(b), except using the compound of Example 19(a), the title compound was prepared. NMR(CDCl₃) δ 6.90 (2H₇ s), 5.00-4.50 (2H, br s), 4.00 (1H, t, J=5 Hz), 2.00-1.70 (2H, m), 1.00-0.80 (3H, m).

- c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-ethyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide
- Following the procedure of Example 1(c), except using

 (2R, 4S, 5S)-5-(t-butoxycarbonyl) amino 4-t-butyldimethylsiloxy6-phenyl-2-phenylmethylhexanoic acid and the compound of
 Example 19(c), the title compound was prepared. NMR (CDCl₃) δ

 7.35-6.90 (10H, m), 6.78 (2H, s), 6.20 (d, J=5 Hz), 4.80-4.65

 (2H, m), 4.05 (1H, q, J=5 Hz), 3.72 (1H, dd, J=10, 3 Hz),

 10 2.90-2.50 (5H, m), 2.10-2.05 (1H, m), 1.90-1.65 (3H, m), 1.40

 (9H, s), 0.95 (9H, s), 0.90-0.85 (3H, m), 0.50 (6H, s).
 - d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-ethyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-

10 88 (LAP & L. B. AL.) 28 3 12

15 hexanamide

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Following the procedure of Example 9(d), except using the compound of Example 19(c), the title compound was prepared. NMR(CD3OD) & 7.40-7.00 (10H, m), 6.85 (2H, s), 3.60-3.50 (2H, m), 2.95-2.60 (5H, m), 1.95-1.52 (4H, m), 1.48-1.26 (9H, m), 0.8-0.9 (3H, m).

MS m/e 521.2 [M+H]+; 503.4, 447.4.

Example 20 tar made :

Part 1 m w Water-a- (3) Flate

- Following the procedure of Example 19(a)-19(d), except substituting Cbz-(L)-α-propylglycinal for Cbz-(L)-α- ε ethylglycinal, the title compound was prepared. Data for the intermediates of this synthesis were:

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(18)-1-carbobenzyloxyamino-1-propyl-1-(imidazol-2-yl)methane. NMR(CDCl3) & 7.40-7.10 (10H, m), 6.65 (2H, s), 5.27 (20 5.55 (1H, d, J=6 Hz), 5.10-4.90 (2H, m), 4.65 (1H, q, J=5 Hz), 2.05-1.93 (1H, m), 1.90-1.75 (1H, m), 1.45-1.20 (4H, m), 6.5 (0.95-0.85 (3H, m), 1.90-1.75 (1H, m), 1.45-1.20 (4H, m), 6.5 (0.95-0.85 (3H, m), 6.65 (2H, m), 6.65 (2H, m), 6.65 (2H, s), 6.65 (2H, s),
```

- b) (1S)-1-(imidazol-2-yl)butylamine. NMR(CDCl₃) δ 6.90 (2H, -(s), 5.10-4.40 (2H, s(br)), 4.05 (1H, t, J=5 Hz), 1.90-1.55 (2H, m), 1.45-1.20 (4H, m), 0.95-0.80 (3H, m).
- 6.c) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-propyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide. NMR(CDCl₃) δ 7.35-7.00 (10H, m), 6.78 (2H, s), 6.22 (1H, d, J=5 Hz), 4.85-4.68 (2H, m), 4.00 (1H, q, J=3 Hz), 3.75 (1H, dd, J=10, 3 Hz), 2.80-2.50 (5H, m), 2.12-1.95 (1H, m), 1.90-1.60 (3H, m), 1.40-1.20 (13H, m), 0.90 (9H, s), 0.87-0.80 (3H, m), 0.07 (6H, s).
 - d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-20 propyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide. NMR(CD3OD) δ 7.40-7.00 (10H, m), 6.90 (2H, s), 3.78-3.50 (2H, m), 2.90-2.60 (5H, m), 1.90-1.55 (4H, m), 1.45-1.20 (13H, m); MS m/e 535.4 [M+H]⁺.

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#: (2.1) and land to the tadden bring which it is the property of the property of the property of the phenyl-2-phenylmethyl-hexanamide

(H2) 18 a) (18)-N-1-(4-bromoimidazol-2-yl)-2-methylpropylacetamide . The Bark and 60.00.00 (CH 6.5) is 60.00 (CH 6.5).

(1S)-N-1-(4,5-dibromoimidazol-2-yl)-2-methylpropylacetamide

35-S methylpropylacetamide (1.58 g, 8.73 mmol) in 95% ethanol (30 mL), 2,4,4,6-tetrabromocyclohexadienone (3.93 g, 9.60 mmol) was added. The resulting mixture was stirred at room temperature for 30 min, and was concentrated in vacuo. The

residue was dissolved in dichloromethane; washed with aqueous NaHCO3 and dried over Na2SO4. The solvent was removed in vacuo, and the residue was purified by flash chromatography (1) (1) 3 to afford the title compound (650 mg, 29%) 10 NMR (CDCl3) δ

5 7.70 (1H, d, J=7 Hz), 6.85 (1H, s), 4.67 (1H, t) J=7 Hz), 2.35-2.25 (1H, m), 1.95 (3H, s), 1.05 (3H, d, J=5 Hz), 0.80

Also isolated was (1S)-N-1-(475-dibromoimidazol-2-yl)-2methylpropylacetamide (50 mg, :8%): : NMR (CDCl3), δ.4.68 (1H, t, J=7 Hz), 2.38-2.25 (1H, m), 2.05 (3H, s), 1.05 (3H, d, J=5 Hz), 0.85 (3H, d, J=5 Hz); MS m/e 340:0 [M+H] +, 280.8.

b) (1S)-1-(4-bromoimidazol-2-yl)-2-methylpropylamine, dihydrochloride (1021, m), 6 70 (21t, s)

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Following the procedure of Example 18(c), except using (1S)-N-1-(4-bromoimidazol-2-yl)-2-methylpropylacetamide, the title compound was prepared. NMR(CD3OD) (5,7.60 (1H, s), 4.35 (1H, d, J=7 Hz), 2.50-2.38 (1H, m), 1.10 (3H, d, J=5 Hz), 0.82 (3H, d, J=5.Hz). property about 18 12(38 34,000) (b)

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c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t- 9 butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-bromoimidazol-2yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 1(c), except using (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-25 6-phenyl-2-phenylmethylhexanoic acid and (1S)-1-(4bromoimidazol-2-yl)-2-methylpropylamine dihydrochloride, the title compound was prepared. NMR(CDCl3) 8 7.40-7.00 (10H, m), 6.70 (1H, s), 6.45 (1H, d, J=5 Hz), 4.80 (1H, d, J=6 Hz), 4.40 (1H, t, J=5 Hz), 4.02 (1H, q, J=4 Hz), 3.78 (1H, dd, J=7, 2 Hz), 2.90-2.30 (9H, m), 1.85-1.60 (2H, m), 1.45 (9H, s), 1.00 (9H, s), 0.85 (6H, t, J=4 Hz), 0.10 (6H, d, J=6 Hz).

d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6-phenyl-2-ag

- - 2. Alien E. Miller - C. B. L. W. (C.).

phenylmethyl-hexanamide or a new ment (ATA) ((c) 65)

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Following the procedure of Example 9(d) except using (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1!-isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide, the title compound was prepared. NMR(CDCl₃) δ 7.40-7.00 (10H, m), 6.70 (1H, s), 6.55 (1H, m), 4.90 (1H, d, J=5 Hz), 4.50 (1H, t, J=5 Hz), 3.75-3.55 (2H, m), 2.95-2.65 (5H, m), 2.40-2.25 (1H, m), 1.90-1.60 (2H, m), 1.48 (9H, s), 0.80 (6H, t, J=6 Hz). MS m/e 613.2 [M+H]+; 535.2.

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Example 22

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4.5-dibromoimidazol-2-yl)]methyl6-phenyl-2-phenylmethyl-hexanamide

(i.e. 15) pages. Following the procedures of Examples 18(c)-18(d), and 18(g) (d), except substituting (1S)-N-1-(4,5-dibromoimidazol-2-colors (yl)-2-methylpropylacetamide for (1S)-N-(1-4-nitroimidazol-2-colors (yl)-2methyl) propylacetamide, the title compound was prepared.

All Analytical data for the intermediates of this synthesis were:

a) (1S)-1-(4,5-dibromoimidazol-2-yl)-2-methylpropylamine, dihydrochloride: NMR(CD3OD), 8 4.10-3.90 (1H, br s), 2.30--35.7 6 2.10 (1H, s(br)), 1.10 (3H, d, J=5 Hz), 0.85 (3H, d, J=5 Hz).

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(325) b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyl
(326) b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyl
(327) dimethylsiloxy-N-[1'-isopropyl-1'-(4, 5-dibromoimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide. NMR (CDCl₃) δ

(328) (328) (329)

bios c) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-35 a isopropyl-1'-(4,5-dibromoimidazol-2-yl)] methyl-6-phenyl-2-, (phenylmethyl-hexanamide. NMR(CDCl3) & 7.35-6.85 (10H, m), 6.65 (1H, br s), 4.92 (1H,1d, J=4 Hz), 4.50 (1H, m), 3.72-, 3.50 (2H, m), 2.98-2.63 (5H, m), 2.15-2.02 (1H, m), 1.90-1.70

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(2H, m), 1.40 (9H, s); MS m/e 693.03 [M+H]+; 637; 619, 593, 575, 291.

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way to be Example 23 Also agreed &

1. (a. 10) (a.7 (a. 11) (a.1-00.1.

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-methylimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide

10

a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4-1339) methylimidazol-2-yl)methane.

Cbz-(L)-valinal (1.0 g, 3.9 mmol) and pyruvaldehyde (4.3 mmol, 40% in H₂O) were dissolved in methanol (10 mL) and chilled in an ice bath. Concentrated aqueous ammonia (2 mL) was added and the reaction mixture was stirred at 20°C overnight. The solvent was removed in vacuo and the residue dissolved in 5% HCl (50 mL) and extracted with ethyl acetate (3x20 mL). The aqueous layer was basified to pH 10 with solid Na₂CO₃. A tan solid (463 mg) precipitated. The solid was purified by flash chromatography (silica, 2%-3% methanol/dichloromethane) to yield the title compound as a white solid (180 mg, 16%). mp 163-164°C; NMR(CDCl₃) & 7.45-

7.35 (5H, m), 6.60 (1H, s), 6.00 (1H, d, J=4 Hz), 5.05 (2H, g, J=4 Hz), 4.40 (1H, t, J=4 Hz), 2.45-2.30 (1H, m), 2.20 (3H, s), 0.95 (3H, d, J=4 Hz), 0.80 (3H, d, J=4 Hz); MS m/e 575.4 (2M+H)+, 288.0 [M+H]+.

b) (2R, 4S, 5S, 1°S) -5-(t-butoxycarbonyl) amino 4-t-13 butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-methylimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 1(b)-1(c), except using (2R,4S,5S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid and the compound of Example 23(a), the title compound was prepared. NMR(CDCl₃) δ 7.37-6.90 (10H, m), 6.45 (1H, s), 6.38 (1H, d, J=3 Hz), 4.75 (1H, d, J=5 Hz), 4.40 (1H, t, J=5 Hz), 3.95 (1H, q, J=4 Hz), 3.72-3.68 (1H, m); 2.90-2.70 (4H,

m), 2.60-2.48 (1H, m), 2.45-2.30 (1H, m), 2.17 (3H, s), 1.90-1.80 (1H, m), 1.75-1.62 (1H, m), 1.40 (9H, s), 0.95 (9H, s), 0.75 (6H, t, J=3 Hz), 0.10 (6H, d, J=2 Hz).

isopropyl-1'-(4-methylimidazol-2-yl)]methyl-6-phenyl-2phenylmethyl-hexanamide

The compound of Example 23(b), the title compound was

10 prepared. NMR(CDCl₃) δ 7.38-7.00 (10H, m), 6.52 (1H, s),

(4.92 (1H, d, J=5 Hz), 4.42 (1H, t, J=4 Hz), 3.72-3.55 (2H,

(2H, br s), 1.42 (9H, s), 0.75 (6H, d, J=3 Hz); MS m/e 549.2

[M+H]+.

15

Example 24

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-trifluoromethylimidazol-220 yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4-trifluoromethylimidazol-2-yl) methane.

trifluoromethylimidazol-2-yl)methane. (m, NI) OT. Sodium acetate trihydrate (5.35 g, 2.2 eq) was dissolved 25 in water (16 mL) and 1,1 dibromotrifluoroacetone (5.31 g, 1.1 eq) was added. The solution was stirred for 30 min at 90°C. The solution was cooled to 0°C and poured into a 0°C solution of Cbz-Valinal (4.22 g, 1.0 eq) in anhydrous methanol (80 mL). Concentrated ammonium hydroxide (22 mL) was added and 30 the mixture stirred overnight at room temperature. The solvents_were evaporated to give a white precipitate, which was covered with 150 mL of water. The suspension was filtered. and the solid washed twice with water. The white solid was dissolved in ethyl acetate, dried over sodium sulfate, filtered, and evaporated to a white solid (5.24, g,, 86%). 1HNMR (CD3OD) & 7.45 (1H, s), 7.40-7.20 (5H, m), 5.05 (2H, q, J=4 Hz), 4.50 (1H, d, J=4 Hz), 2.38-2.10 (1H, m), 1.00 (3H, He) 00 d, J=4 Hz), 0.80 (3H, d, J=4 Hz), 13CNMR (CD3OD, 1H-decoupled)

20

δ 18.9, 19.4, 67, 117 (q, J=3 Hz), 123.2 (q, J=266 Hz), 128.7, 129.3, 133 (q, J=39 Hz), 138.0, 151.7; MS m/e 342.0 [M+H]+.

b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyl-dimethylsiloxy-N-[1'-isopropyl-1'-(4-trifluoromethylimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 1(b)-1(c), except using the compound of Example 24(a) and (2R, 4S, 5S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid, the title compound was prepared.

NMR(CDCl₃) & 7.35-6.95 (11 H, m), 6.50 (1H, d, J=4 Hz), 4.75 (1H, d, J=6 Hz), 4.25 (1H, t, J=4 Hz), 3.95 (1H, q, J=4 Hz), 3.80-3.68 (1H, m), 2.90-2.40 (5H, m), 1.80-1.60 (2H, m), 1.35 (9H, s), 0.90 (9H, s), 0.80 (3H, d, J=3 Hz), 0.70 (3H, d, J=3 Hz), 0.05 (6H, d, J=2 Hz).

c) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-isopropyl-1'-(4-trifluoromethylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 9(d), except using the compound of Example 24(b), the title compound was prepared. NMR(CDCl₃) & 7.35°(1H, s), 7.25-6.90°(10H, m), 4.53 (1H, d, J=5 Hz), 3.68 (1H, t, J=4 Hz), 3.52 (1H, d, J=6 Hz), 2.90-2.55 (5H, m), 2.10-1.95 (1H, m), 1.85-1.70 (1H, m), 1.65-1.50 (1H, m), 1.40-1.25 (9H, m), 0.90°(3H, d, J=4 Hz), 0.65 (3H, d, J=4 Hz); MS m/e 603.2 [M+H]⁴, 529.2, 503.2.

Example 25) Land of sold to the house is beginning the first of the fi

- Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-methyl-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-phenylmethyl-hexanamide
- a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(imidazol-2-yl)methane

Following the procedure of Example 1(a), except substituting N-methyl-Cbz-(L)-valinal for Cbz-(L)-valinal, the title compound was prepared. NMR(CDCl3) 8 7.45-7.30 (5H,

m), 6.90 (2H, s), 5.12 (2H, s), 4.60 (1H, d, J=6 Hz), 2.95 (3H, s), 2.70-2.53 (1H, m), 1.02 (3H, d, J=3 Hz), 0.85 (3H, d, J=3 Hz).

5.1 b) (1S)-1-methylamino-1-isopropyl-1-(imidazol-2-yl)methane Following the procedure of Example 1(b), except using the compound of Example 25(a), the title compound was prepared. NMR(CDCl₃) δ 6.95 (2H, s), 3.52 (1H, d, J=3 Hz), 2.30 (3H, s), 2.10-1.90 (1H, m), 0.98 (3H, d, J=3 Hz), 0.82 (3H, d, J=3 Hz).

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- (a) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-methyl-N-(1'-isopropyl-1'-imidazol-2yl) methyl-6-phenyl-2-phenylmethyl-hexanamide
- Following the procedure of Example 1(c), except using the compound of Example 25(b), the title compound was prepared. NMR(CDCl₃) δ 7.40-6.72 (12H, m), 4.82 (1H, d, J=5 Hz), 3.95 (1H, q, J=4 Hz), 3.82-3.75 (1H, m), 2.95-2.70 (5H, m), 2.51 (2H, s), 2.50-2.38 (1H, m), 2.08 (1H, s), 1.87-1.68 (2H, m), 1.38 (9H, s), 0.95 (9H, s), 0.88 (3H, d, J=3 Hz), 0.75:(3H, d, J=3 Hz), 0.05 (6H, d, J=7 Hz).
- d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-leader at methyl-N-(14-isopropyl-14-imidazol-2-yl) methyl-6-phenyl-2, 25 phenylmethyl-hexanamide

have produced that industry or which there is the complete of the control of

Following the procedure of Example 9(d), except using the compound of Example 28(c), the title compound was prepared. NMR(CDCl₃) & 7.35-6.82 (12H, m), 4.90-4.72 (1H, m), 3.70-3.00 (2H, m), 2.92-2.50 (8H, m), 1.90-1.60 (2H, m), 30 1.40-1.30 (9H, m), 0.95-0.70 (6H, m).

MS m/e 549.2 [M+H]⁺.

and decouple to the end . Example 26 to the search

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-carbomethoxyimidazol-2yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

public process, which objects to its ones in the

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a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4- (5- trimethoxymethylimidazol-2-yl)methane:

Sodium methoxide (8 mL, 25% in methanol, 37.5 mmol) was added to a solution of the compound of Example 27(a) (640 mg, 1.88 mmol) in anhydrous methanol (10 mL). The resulting mixture was heated at 55°C overnight, cooled, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and H₂O, and the organic extract was dried over Na₂CO₃. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 2% methanol/dichloromethane) to afford the title compound (545 mg, 77%). NMR(CDCl₃) & 7.40-7.20 (5H, m), 6.98 (1H, br s), 5.90 (1H, br s), 5.08 (2H, s), 4.50 (1H, br s), 3.15 (9H, s), 2.00 (1H, m (br)), 1.00-0.80 (6H, m); MS m/e 378.2 [M+H]⁺, 346, 332, 271, 195.

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b) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4- carbomethoxyimidazol-2-yl)methane

A solution of the compound of Example 26(a) (540 mg) in 1:1 methanol/aqueous HCl (10 mL) was stirred at room temperature for 2 h, and concentrated under reduced pressure. The residue was partitioned between aqueous Na₂CO₃ and dichloromethane, and the organic extract was dried over Na₂CO₃ and concentrated in vacuo to afford the title compound (470 mg, 75%). NMR (CDCl₃) & 7.55 (1H, br₅), 7.35 (5H, s), 5.90-5.65 (1H, m), 5.10 (2H, t, J=4 Hz), 4.60-4.42 (1H, m), 3.88 (3H, s), 2.40 (1H, br s), 1.00-0.80 (6H, m); MS m/e 332.2 [M+H]⁺.

30 c) (1S)-1-amino-1-isopropyl-1-(4-carbomethoxyimidazol-2-2 yl)methane

Following the procedure of Example 1(b), except using the compound of Example 26(b), the title compound was prepared. NMR(CDCl₃) & 7.62 (1H, s), 3.97 (1H, d, J=4 Hz),

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35 3.82 (3H, s), 2.27-2.05 (1H, m), 0.95-0.75 (6H, m) . 35

ELOS d) (2R,4S,5S,1!S)-5-(t-butoxycarbonyl) amino-4-t-butyl10 0 0 dimethylsiloxy-N-[1'-isopropyl-1'-(4-carbomethoxyimidazol-22011 0 0 1] methyl-6-phenyl-2-phenylmethyl-hexanamide
2012 Following the procedure of Example 1(c), except using
2013 the compound of Example 26(c), the title compound was
2014 prepared. NMR(CDCl3) 8,7.45-6.90 (12H, m), 6.48 (1H, d, J=4
21 Hz), 4.72 (1H, d, J=6 Hz), 4.35 (1H, s br), 4.02-3.87 (1H,
21 m), 3.85 (3H, s), 3.75-3.60 (1H, m), 2.90-2.40 (5H, m), 1.9021 1.60 (2H, m), 1.42 (9H, s), 0.90 (9H, s), 0.72 (6H, d, J=4
21 10 Hz), 0.10 (6H, d, J=3 Hz)

EMP (RA 1.1 de 11.0) (SIVE of and 1 for thospilar of

e) (2R, 4S, 5S, 1:S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-c (3) [1'-isopropyl-1'-(4-carbomethoxyimidazol-2-yl)] methyl-6phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 9(d), except using the compound of Example 26(d), the title compound was prepared. NMR(CDCl₃) & 7.40-6.80 (12H, m), 4.90 (1H, d, J=5 2.68 (5H, m), 2.45-2.30 (1H, m), 1.80-1.60 (2H, m), 1.40 (9H, M), 2.00 (S), 00.72 (6H, d, J=40Hz); MS m/e 593.2 [M+H]+, 537.2, 519.2, MS 0.493.2, 475.2.3.4

Example 27

25 1) Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl) amino-4hydroxy-N-[1'-isopropyl-1'-(4-methylcarbonylimidazol-2yl) lmethyl-6-phenyl-2-phenylmethyl-hexanamide

(15) -1-carbobenzyloxyamino-1-isopropyl-1-(4-

30. A hydroxymethylimidazol-2-yl) methane.

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it will at the compound of Example 26(b) (0.314.g, 1.0 eq) was attributed in anhydrous toluene at 78°C under an argon atmosphere. Dissobutylaluminum hydride (3.8 mL, 1.0M in 6.7 kg. Krichexanes, 4.0 eq) was added and the solution stirred at -78°C 2835 for 1 h. The reaction was quenched with methanol (0.2 mL, 1.0 eq). The solution was then diluted with Rochelles salt solution (sat.) and stirred for 1 h. The solution was extracted with dichloromethane twice and the combined organic

extracts were washed successively with saturated aqueous
Rochelles salt and brine. The organic layer was dried over
magnesium sulfate, filtered, and evaporated to give the title
compound as a white solid: (0.27 g/ 94%) MMR(CDCl3) & 7.25

5 (5H, s), 6.69 (1H, s), 6.14 (1H, d), 5.01 (2H, dd), 4.52 (2H, s), 4.37(1H, t), 2.19 (1H, m), 0.92 (3H, d), 0.73 (3H, d); MS
m/e 304.0 [M+H]+...

T. F . (a. 36; 69.5), (a.

b) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4-0%.

f (v) () () (H)) (6)

10 formylimidazol-2-yl)methanel Robert Ab (Re), Of O a (RR 01

The compound of Example 27(a) (0.11 g, 1.0 eq) was stirred in anhydrous dichloromethane at room temperature under an inert argon atmosphere. Manganese dioxide! (0.126 g, 4.0 eq) was added and the mixture was stirred at room temperature overnight. After 16 h and additional 2.0 eq of manganese dioxide was added. The reaction was complete by TLC after 2 h. The mixture was filtered through a pad of Celite® and the filter cake was washed with dichloromethane. The organic solvent was removed in vacuo to give the title compound as a white solid (0.075 g, 69%).) NMR(CDCl3) & 9.57 (1H,s), 7.54 (1H, s), 7.12 (5H, s), 6.43 (1H, d), 4.96 (2H, dd), 4.43 (1H, t), 2.08 (1H, m), 0.91 (3H, d), 0.62 (3H, t); MS m/e 302.0 [M+H]+.

c) (1s,1'Rs)-1-carbobenzyloxyamino-1-isopropyl-1-(4-(1'-hydroxyethyl)imidazol-2-yl)methane.

The compound of Example 27(b) (0.1 g, 1.0 eq) was stirred in a 3:1 ether/THF mixture at 0°C under an argon atmosphere. Methyl magnesium bromide (0.47 mL, 3.0M in THF, 4.0 eq) was added and allowed to stir at 0°C for 1.5 h. The solution was diluted with 5% aqueous HCl and made basic with solid sodium carbonate. The solution was extracted with ethyl acetate three times and the combined organic extracts were dried over sodium carbonate, filtered, and evaporated to a white solid (0.1 g, 95%). NMR(CDCl3) & 7.19 (5H,s), 6.59 (1H, s), 6.42 (1H, d), 4.92 (2H, dd), 4.73 (1H, m), 2.09 (1H, m), 1.37 (3H, d), 0.82 (3H, d), 0.66 (3H, d).

d) (1S, 1'RS)-1-amino-1-isopropyl-1-(4-(1'-hydroxyethyl)imidazol-2-yl)methane.

bit d), 0.84 (3H, d), 0.67 (3H, d).

stirred in anhydrous methanol with 10% Pd on activated carbon (0.020 g). Hydrogen gas was bubbled through the solution via balloon for 1 h and the reaction was maintained under a hydrogen atmosphere for 3 h. The mixture was filtered through a pad of Celite® and the filter cake washed with methanol. The methanol was evaporated to give the title compound as a white solid (0.05 g, 87%). NMR (CDCl3) & 6.63 (1H, 8),44.72 (1H, dd), 3.61 (1H, d), 1.92 (1H, m), 1.49 (3H,

2- 7 e) (2R, 4S, 5S, 1'S, 1'!RS) -5-(t-butoxycarbonyl) amino-4-t-

Carlo Carlo Carlo Region (Art. Service) (According to the Carlo Ca

butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-(1''-hydroxyethyl)imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

To a solution of (2R,4S,5S)-5-(t-butoxycarbonyl)amino-4t-butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid (0.131-g,(1.0 eq) in anhydrous dimethylformamide, the

compound of Example 27(d) (50 mg, 1.1 eq), BOP reagent (0.11 g, 1.0 eq), and triethylamine (0.04 mL, 1.0 eq) were mover dadded. The solution was stirred at room temperature for (1.12 times with dichloromethane. The combined organic extracts

were washed with water, then brine. The solution was dried over magnesium sulfate, filtered, and evaporated to give a white foam. In The foam was chromatographed (silica, 4%)

od le compound as a white foam (0:11.g, :65%). NMR(CDCl3) & 7.31-6.54 (12H, m),

0.1 (1H, d), 4.48 (2H, d), 3.82 (1H, q), 3.61 (1H, m), 2.81-0.1 (-2.3)(6H, m), 01.65 (3H, m), 1.48 (3H, d), 1.22 (9H, s), 0.89 0.0 (9H, s), 0.70 (3H, d), 0.61 (3H, d), 0.06 (6H, s); MS m/e

693.4 [M+H] * 1.041 | 5.00 Pt - 1/4 | 1/4 | 1/4 | 1/4 | 1/4 |

∴ 25°

f) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t- (butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-methylcarbonylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

The compound of Example 27 (e) (45 mg, 1.0 eq) was stirred in dry dichloromethane under an inert argon atmosphere. Manganese dioxide (23 mg, 4.0 eq) was added and the mixture was stirred at room temperature for 16th. An additional 2.0 eq of manganese dioxide was added and the reaction was complete by TLC after 2.5 h. The mixture was filtered through a pad of Celite® and the filter cake was washed with dichloromethane. The organic solvent was evaporated to give the title compound as a white solid (0.038 g, 85%). NMR(CDCl₃) δ 7.49-6.76 (11H, m), 6.30 (1H, br d), 4.71 (2H, m), 3.86 (1H, q), 3.61 (1H, dd), 2.77-2.41 · 15 · (5H, m), 2:31 (3H, s), 1:58 (2H, m), 1:20 (9H, s), 0:83 (9H, s), 0.69 (6H, dd), 0.04 (6H,d); MS m/e 691.4 [M+H]+.

g) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'isopropyl-1'-(4-methylcarbonylimidazol-2-yl)]methyl-6-phenyl-

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The compound of Example 27(f) (38 mg, 1.0 eq) was stirred in anhydrous THE under an argon atmosphere at room temperature. Tetrabutyl ammonium fluoride (0.33 mL, 1.0M in THF, 6.0 eq) was added and the solution stirred for 16 h. The solution was diluted with water and extracted three times with dichloromethane. The combined organic extracts were washed with water and evaporated to adwhite solid. The solid was covered with diethyl ether, decanted twice, and dried to igive the title compound as a white solid (250mg p579%).

30 NMR (CDCl3) 8 7.14 (5H, m), 6.86 (5H, m), 5.14 (1H, d), 4.42 (1H, d), 3.58 (1H, q), 3.45 (1H, d), 2.80-2.50 (5H, m), 1.91 (1H, m), 1.63 (2H, m); 1.26.(9H, s) ((rotamer observed), 0.70 (3H, d), 0.57 (3H, d); MS m/e 577.2 [M+H]+.

Example 28

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-isopropylcarbonylimidazol-2-5 yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

price a) (1S, 1'RS)=1-carbobenzyloxyamino-1-isopropyl-1-(4-(1'palifies hydroxy-2'-methyl) propylimidazol-2-yl) methane.

ed: hydroxy-2'-methyl) procedure of Example 27(c), except using

(*10 isopropyl magnesium bromide (1.024 mL, 2.0M solution, 4.0 eq)

in place of methyl magnesium bromide, to yield a crude

product. The crude product was chromatographed (silica, 4%

methanol/dichloromethane) to yield the title compound as a

white solid (0.155 g , 88%) NMR(CDCl3) & 7.19 (5H, m), 6.58

15 (1H, s), 4.91 (2H, m), 4.38 (1H, q), 4.20 (1H, dd), 2.11 (1H,

m), 1.83 (1H, m), 0.72 (12H, m); Ms m/e 346.2 [M+H]+; 328.2,

279.0 , 254.0, 205.0, 177.0, 149.0, 118.0

igi = 10b) (1S,1!RS)-1-amino-1-isopropyl-1-(4-(1'-hydroxy-2'-b)20 g methyl) propylimidazol-2-yl) methane

ie.7 6 ((100)) Following the procedure of Example 27(d), using the compound tof Example 31(a), the title compound was prepared as alwhite foam (96 mg, (100%). NMR(CDCl3) δ (6.65 (1H, s), 4.21c(1H/rd), 3.90 (1H, s), 2.22 (1H, m), 1.94 (1H, m), 0.93 colors (6H, m); 0.64 (6H, m); MS m/e 302.0 [M+H]+.

the compound of Example 31(b) (96 mg, 1.1 eq), substituting dimethyl formamide as the solvent instead of dichloromethane, t and purifying the product by chromatography, the title

35 compound was prepared (168 g, 57%). NMR (CDCl₃) δ:7.22-6.81 =(11H, m) / 6.62 (1H, dd), 4.71 (1H, dd), 4.53 (1H, t), 4.19 - (1H, d), 3.82 (1H, q), 3.58 (1H, dd), 2.71-2.30 (5H, m), 2.03 - (2α(1H, m), 1.70 (1H, m), 1.57 (1H, m), 1.14 (9H, s), 0.91 (3H, d), 0.88 (9H, s), 0.78 (3H, d), 0.67 (3H, d), 0.59 (3H, d), 0.03 6H, d); MS m/e 721.4 [M+H]+. The second secon

d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-isopropylcarbonylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide Following the procedure of Example 27(f) Plexcept using the compound of 31(c) (168 mg, 1.0 eq) and chromatographing the crude product (silica, 13%) methanol/dichloromethane) the title compound was prepared as a white solid (132 mg, 79%). NMR (CDCl₃) & 7.20-6.76 (11H, m) .m5.05 (1H, 5br₃m), 3.88 (1H, g), 3.61 ; m), 3.19 (1H, m), 2:80-2.46 (5H, m); #2.22 (1H, m), 2.07 (1H, m), 1.63 (1H, m), 1.15 (16H, m), 0.89! (9H, s), 30.74 (6H, m), 0.08 (6H, d); MS m/e 719.4 [M+H]+11 is LAND TO THE MEDITAL AND THE SECOND

(1) 15 2.1.2

e) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'isopropyl-1'-(4-isopropylcarbonylimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 27(g), except using the compound of Example 31(d) (132 mg); the title compound 20 was prepared as a white foam (90 mg, 81%) NMR (CDCl3) & 7.48 (1H, s), 7.11 (5H, m), 6.82 (5H, m), 5.29 (1H, d), 54.46 (1H, m), 3.54 (1H, q), 3.48 (1H, m), 3.148 (1H, m), 2.74-2.44 (5H, (1.61.(2H/km)), 1.28.(9H/ks) (rotamers observed), 1.13 (6H, m), 0.69 (3H, d), 0.48 (3H, d); MS m/e 605.2 [M+H]+.

(20, 48, 48, 115, 117, 17, 17, 18, 18, 18) Example 29 / le (videmi). (c)

- Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-phenylcarbonyl-imidazol-2yll lmethyl-6-phenyl-2-phenylmethyl-hexanamide A. B. of Dec. 182 as infimiorall Lytischelle
- a) (1S,1'RS)-1-carbobenzyloxyamino-1-isopropyl-1-(4-(1'hydroxy) benzylimidazol-2-yl) methane hydroxy boungers

Following the procedure of Example 27(c)/ except substituting phenylmagnesium bromide (0.45 mL, 3.0M solution, 4.0 eq) for methyl magnesium bromide, and chromatographing

The second of th

the crude product (silica, 3% methanol/dichloromethane) the title compound was prepared as a white solid (175 mg, 96%).

NMR (CDCl₃) & 7.26 (1H, d), 7.11 (10H, m), 6.39 (1H, dd), 6.08

(1H, d), 5.63 (1H, d), 4.82 (2H, m), 4.29 (1H, m), 2.01 (1H, 5 m), 0.76 (3H, m), 0.59 (3H, d).

- the compound of Example 29(a) (98 mg) the title compound was prepared as a tacky white foam (65 mg, 98%).

arian in a

hexanamide hexanamide

Following the procedure of Example 27(e), except using the compound of Example 29(b) (0.065 g, 1.1 eq), and chromatographing the crude product (2% methanol/

- 20 dichloromethane) the title compound was prepared as a white bring solid (109 mg, 55%). NMR(CDCl₃) δ 7.48-6.79 (16H, m), 4.77 (1H, m), 3.88 (1H, m), 3.61 (1H, m), 2.65 (4H, m), 2.39 (1H,
 - (1H, m), 2.15; (1H, m), (1.94 (1H, m), 1.75 (1H, m), 1.56 (1H, m), 1.21 (9H, s) (rotamers observed), 0.86 (9H, s), 0.68 (6H, 25 dd), 0.07 (6H, s); MS m/e 755.4 [M+H]+.

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- d):(2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-t-butyl-dimethylsiloxy-N-[1!-isopropyl-1!-(4-phenylcarbonylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide
 ph30.qp:print Following the procedure Example 27(f), except using the
 compound of Example 29(c) (109 mg, 1.0 eq), the title
 compound was prepared as a white solid (80 mg, 74%).
- NMR (CDC13) & 7.49-6.84; (17H, m), 3.88 (1H, q), 3.63 (1H, t), (1d) 08 2.87-2.49; (6H, m), 2.11 (2H, m), 1.64 (1H, m), 1.11; (9H, s), (35,); 0.82 (9H, s), 0.71; (6H, dd), 0.06; (6H, d); MS m/e 753.4; (0.4, (M+H)+.33.4); MS m/e 753.4;

(1) × 100)

- e) (2R,4s,5s,1's)-5-(t-butoxycarbonyl) amino 4-hydroxy-N-[1'-isopropyl-1'-(4-phenylcarbonylimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide
- Following the procedure of Example 27(g) except using
 - 5 the compound of Example 29(d) (80 mg, 1.0 eq), the title compound was prepared as a white solid (45 mg, 74%).

 NMR(CDCl₃) δ 7.84-6.77 (16H, m), 4.48 (1H, d), 3.59 (1H, m), 3.42 (1H, m), 2.80-2.54 (5H, m), 1.99 (1H, m), 1.63 (2H, m),
 - 1.26 (9H, s) (rotamers observed), 0173 (3H, d); 0.59 (3H, d);
 - 10th MS m/e 639.2 [M+H]+. W) (15%) of contact to be writing of the

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Example 30

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4
1 15 hydroxy-N-[1'-isopropyl-1'-(4-formylimidazol-2-yl)|methyl-6
phenyl-2-phenylmethyl-hexanamide

- a) (1S,1'RS)-1-amino-1-isopropyl-1-(4-(hydroxy) methyl-imidazol-2-yl) methane. Or a charge and palaton polamorulo
- The compound of Example 27(a) (90 mg), the titled compound was prepared (50 mg, 100%). NMR(CDCl3) & 6.85 (1H, 1s), 4.62 (2H, s), 3.85 (1H, d, J=4 Hz), 2.20-2.05 (1H, m), 0.88 (6H, d, J=5 Hz).

25 (2.2). 10 s\n SM (8 (10) V0.0 , 55

- b) (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-(hydroxy) methyl-imidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide
- Following the procedure of Example 27(e) ym except using the compound of Example 30(a) (50 mg), and chromatographing the crude product (silica, 2% methanol/dichloromethane) the title compound was prepared (130 mg, 65%)... NMR (CDCl3) &
- 7.30-6.95 (11H, m), 4.82 (1H, d), 4.50-4.60 (1H, m), 4.40 (1H, d), 3.90-4.00 (1H, m), 3.60-3.68 (1H) m), 2.45-2.80 (5H,
 - 35 m), 2.20-2.30 (1H, m), 1.75-1.85 (1H, m), 1.60-1.70 (1H, m), 1.30 (9H, s), 0.95 (9H, s), 0.75 (3H, d), 0.62 (3H, d), 0.05 (6H, d).

- c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-[1'-isopropyl-1'-(4-formylimidazol-2yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide
- Following the procedure of Example 27(f), except using the compound of Example 30(b) (50 mg), the title compound was prepared (20 mg, 40%). NMR(CDCl₃) δ 9.80(0.5H, s), 9.64

 (0.5H, s), 7.50-6.90 (11H, m), 6.52-6.42 (1H, m), 4.88-4.70

 (2H, m), 4.42-4.32 (1H, m), 4.02-3.93 (1H, m), 3.78-3.71 (1H, m), 2.90-2.40 (5H, m), 2.30-2.19 (1H, m), 1.87-1.62 (2H, m),
- 1000010 1.450(9H, s), 0.95 (9H, s), 0.87-0.72 (6H, m), 0.05 (6H, m) (rotamers).

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d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'isopropyl-1'-(4-formylimidazol-2-yl)]methyl-6-phenyl-2phenylmethyl-hexanamide of ...o.

Following the procedure of Example 27(g), except using the compound of Example 30(c) (20 mg), the title compound was prepared (12 mg, 71%). NMR(CD3OD) & 9.60 (1H, s), 7.65 (1H, s), 7.20-6.90 (10H, m), 4.52 (1H, d), 3.60 (1H, m), 3.45 (1H, d), 2.80-2.45 (5H, m), 2.00-1.88 (1H, m), 1.75-1.65 (1H, m), (11.62-1.45)(1H, m), 1.27 (9H, s), 0.82 (3H, d), 0.62 (3H, d); MS m/e 563.4, 242.2, 204.8:

Example 31

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-(hydroxymethyl)-imidazol-2yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

the compound of Example 30(b) (40 mg), the title compound was prepared (20 mg)., NMR(CD3OD) & 7.27-6.92 (10H, s), 6.72 (1H, coses) (20 mg)., NMR(CD3OD) & 7.27-6.92 (10H, s), 6.72 (1H, coses) (20 mg)., NMR(CD3OD) & 7.27-6.92 (10H, s), 6.72 (1H, coses) (20 mg)., 1.28 (1H, d), 2.82-2.50 (1H, m), 1.78-1.67 (1H, m), 1.63-1.49 (1H, 35.0 m), 1.28 (9H, s), 0.80 (3H, d), 0.65 (3H, d); MS m/e 565.4.

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y(m ,RC) 1955.8-85 6 (ja 1982-60. 1966.) (to j 12 90.5) is

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but of dimethylacily-M-(1 - de opers - 1 1- (4 - g - g - c)

Preparation of (2R.4S.5S.1'S)-5-((tetrahydrothiopyran-4yl)oxycarbonyl)amino-4-hydroxy-N-(14-isopropyl-1'-imidazol-2sta 5 v1) méthyl-6-phenyl-2-phenylmethyl-hexanamide mon sain a nreprinted (20 mg, 10%). Rocketonic, & S. t. t. St., 30, 40

Following the procedures of Example 14 (a)-14 (c), except using 4-hydroxytetrahydrothiopyran in place of 2benzyloxyethanol, the title compound was prepared. Analytical data for the intermediates of this synthesis were: ing in leasanger)

a) (tetrahydrothiopyran-4-yl)-(4-nitro)phenylcarbonate. NMR (CDCl₃) δ 8.26 (1H, s) % 8.22 (1H, s) % 27.38 (1H, s) , 7.33 (1H, s), 4.79 (1H, m), 2.90-2.75% (2H, m), 2.70-2.52 (2H, m), 2.31-2.16 (2H, m), 2.10-1.90 (2H, m) ver - Lydrenivassky collecting the process as at a range of the

b) (2R,4S,5S,1'S)-5-((tetrahydrothiopyran-4-yl)oxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-phenylmethyl-hexanamide. NMR (CD3OD) 8 7.12-6.65 20 (10H, m), 6.64 (2H, s), 5.60 (1H; d), 4.362(2H, 2m), 3.58 (1H, q), 3.49 (1H, d), 2.68-2.48 (6H, m), 2.44-2.30 (3H, m), 1.93-

Example 33

1.74 (3H, m), 1.70-1.40 (4H, m), 0.61 (3H, Ed), 0.50 (3H, d).

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Preparation of (2R.4S.5S.1'S)-5-((tetrahydro-4R-pyran-4vl) oxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2yl) methyl-6-phenyl-2-phenylmethyl-hexanamide

- 0.130 Following the procedures of Example 14(a)-14(c), except using 4-hydroxytetrahydro-4H-pyran in place of 2- 343 Sec. 25. 1 benzyloxyethanol, the title compound was prepared. Analytical data for the intermediates of this synthesis were: on the second of the second of the second se
 - 35 a) (tetrahydro-4H-pyran-4-yl)-(4-nitro)phenylcarbonate... NMR (CDCl₃) δ 8.32 (1H, s), 8.28 (1H, s), 7.41 (1H, s), 7.38 (1H, s), 5.00 (1H, m), 4.05-2.90 (2H, m), 3.68-3.49 (2H, m), 2.17-2.00 (2H, m), 1.95-1.75 (2H, m).

```
b) (2R, 4S, 5S, 1'S) -5-((tetrahydro-4H-pyran-4-yl) oxycarbonyl) -
amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-
phenyl-2-phenylmethyl-hexanamide. NMR(CD3OD) & 7.16-6.89

(10H, m), 6.79 (2H, s), 4.54 (2H, m), 3.82-3.70 (2H, m),
3.69-3.62 (1H, m), 3.50-3.46 (1H, m), 3.45-3.35 (2H, m),
(2.79-2.65 (4H, m), 2.64-2.45 (3H, m), 2.00 (1H, m), 1.82-1.62
(3H, m), 1.55-1.45 (2H, m), 1.37 (1H, m), 0.79 (3H, d), 0.63
(3H, d).
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in correspond (por the control of the Example 34) and the

Preparation of (2R,4S,5S,1'S)=5-(4-picolinyloxy)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

The compound of Example 1(d) was dissolved in neat TFA.

(1) After 10 min the solution was concentrated to provide the

amine salt, \((2R,4S,5S,1!S)-5-amino-4-hydroxy-N-(1!-isopropyl-

20 1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

-Lydiow trifluoroacetate. (This maine salt (25 mg, 1 eq) was

from dissolved in DMF, and (4-picolinium-(p-nitro)phenyl carbonate

price appointrophenylate (23 mg, 1) eq) and triethylamine (0.04 mL, 5

bind on eq) (were added, or The mixture was stirred under Ar for 17 h.

0% . I 25 (% Water was added and the mixture (was extracted with

barrowers of the order over

dichloromethane. The organic extracts were concentrated and the residue was triturated with ether to yield the title compound (20 mg, 61%). NMR(CD₃OD) δ 8.52 (2H, d), 7.10 (14H, m), 6.87 (2H, s), 5.07 (2H, dd), 4.61 (1H, d), 3.80 (1H, m), 30. 3.59 (1H, m), 2.77 (5H, m), 2.05 (1H, m), 1.83 (1H, m), 1.60

MS m/e570.5% [M+H]+Line that the last t

and person ignored (to) I blowski in this lie of a marketing of

-Lyer workbild from () by a (go on t) Example 35 to the process of

The (BS) Preparation of (2R.4S.5S.1'S) -5-(t-butoxycarbonyl) amino-4-

ere with hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

18) 56. (4.4.4-trifluorobut-1-yl) hexanamide

... 20

25

a) (3R,5S,1'S)-(1'-t-butoxycarbonylamino-2'-phenyl)ethyl-3-(4,4,4-trifluorobut-1-yl)-tetrahydrofuran-2-one-les

To a solution of lithium dilsopropyl amide (1.8 mL of a 5 1.5M solution, 2.2 eq) in tetrahydrofuran (10 mL) was added (5S, 1'S)-(1'-t-butoxycarbonylamino-2'-phényl) éthyltetrahydrofuran-2-one (0.50 g: 1.0 eq) in anhydrous THF (2 mL) at -78°C. After stirring for 15 min at (-78°C,) hexamethylphosphoramide (0.57 mL, 2.0 eq) was added to the solution. The solution was stirred for several min and 1,1,1-trifluoro-4-iodobutane (0.78 g, 2.0 eq) was added. After 2 h at -78°C, the reaction mixture was quenched with a 10% aqueous HCl and extracted with dichloromethane. organic extracts were combined and evaporated to a clear oil. The oil was chromatographed (silica, 2% methanol/si dichloromethane) to give the title compound as a white foam (0.248 g, 37%). NMR: (CDCl3) δ 7.18 (5H , m), 4.57 (1H; d), 4.41 (1H , dd) , 3.95 (1H , q) , 2.82 (2H, d) , 12:55 (2H , m) , 2.49-1.49 (7H , m), 1.32 (9H , s); MS m/e 438.0 (M+Na)+.

b) (2R,4S,5S)-5-(t-butoxycarbonyl)amino-4-t-butyldimethyl-siloxy-6-phenyl-2-(4,4,4-trifluorobut-1-yl)hexanoic acid

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Following the procedure of Example 12(b), except using the compound of Example 35(a) (245 mg), the title compound was prepared (215 mg, 67%). NMR(CDCl3) 8 7.18 (5H; m), 4.70 (1H, d), 3.88 (1H, q), 3.69 (2H, m), 2.73 (1H, m), 2.38 (1H, m), 1.91 (2H, m), 1.45 (6H, m), 1.31 (9H, s) (rotamers observed), 0.90 (9H, s), 0.08 (6H, d); MS m/e548.2 [M+H]+.

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c) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-t-butyl-dimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(4,4,4-trifluorobut-1-yl)hexanamide

Following the procedure of Example 1(c), except using the compound of Example 35(b) (100 mg) and (1S)-1-imidazol-2-yl-35 2-methylpropylamine, the title compound was prepared (83 mg, 68%). NMR(CDCl₃) δ 7.22 (5H, m), 7.03 (1H; d), 6.89 (2H, s), 4.72 (1H, d), 4.51 (1H, t), 3.91 (1H, q), 3.65 (1H, m), 2.78 (2H, d), 2.33 (2H, m), 1.82 (4H, m), 1.48 (4H, m), 1.36 (9H,

two singlets; rotamers present), 0.99 (9H, s), 0.91 (3H, d), 0.79 (3H, d), 0.07, (6H, d); MS m/e669.4 [M+H]+.

(2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-(1'-5)isopropyl-1!-imidazol-2-yl)methyl-6-phenyl-2-(4,4,4-trifluorobut-1-yl)hexanamide

Following the procedure of Example 9(d), except using the compound of Example 35(c) (83 mg), the title compound was prepared (40 mg, 58%). NMR(CD3OD) & 7.19 (5H, m), 6.92 (2H, 10 m s), 4.61 (1H, d), 3.64 (1H, q), 3.48 (1H, m), 2.79 (2H, m), 2.49 (1H, m), 2.13 (4H, m), 1.60 (5H, m), 1.36 (9H, s), 0.90 (3H, d), 0.71 (3H, d); MS m/e555.2 [M+H]+.

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Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-(1'-isobutyl-1'-(imidazo-2-yi))methyl-hexanamide hydrochloride

20 10 a) 2-(1'-carbobenzyloxyamino-1'-isobutyl) methyl-imidazole

(1.10 Following the procedure of Example 1(a), except
substituting Cbz-isoleucinal (1.83 g) for Cbz-valinal, the
title compound was prepared (0.658 g, 31%). NMR(CDCl₃) δ

6.96 (2H, s), 5.31 (1H, d), 4.48 (1H, dd), 2.15 (1H, m), 1.44

25 (9H, s), 1.17 (2H, m), 0.92 (3H, t), 0.82 (3H, d); MS

[(DCI/NH₃) m/e 254.2 [M+H]⁺.

b) (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-(1'-isobutyl-1'-(imidazo-2-30 yl))methyl-hexanamide hydrochloride

substituting the procedure of Example 1(b)-1(d), except substituting the compound of Example 36(a) for (1'S)-1'
Miles Carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane,

White the title compound was prepared. NMR (DMSO-d6) 8 7.90 (1H,d),

35 7:29-7:020(10H, m), 6.89:0(2H,s), 6.50. (1H,d), 4.81: (1H,m), 4.55:0(1H,:dd), 3.56 (1H,m), 2.69 (5H,m), 1.80 (1H,m), 1.59 (2H, m), 1.30:1(9H,s), 1.17:0(2H,m), 0.78: (3H, t), 0.63 (3H, d); MS (DCI/NH3) m/e 549.7 [M+H]+...

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-((1RS)-1-hydroxyethyl)imidazol-2-yl) lmethyl-6-phenyl-2-phenylmethyl-hexanamide Tollowing the appropriate of the engineering and publication

The t-butyldimethylsiloxy-protected alcohol from Example 30(e) (20 mg, 1.0 eq) was stirred in anhydrous THF under an argon atmosphere at room temperature. Tetrabutyl ammonium fluoride (0.33 mL of a 1.0M solution in THF, 6.0 eq) was added and the solution stirred for 16 h. The solution was diluted with water and extracted with dichloromethane. combined organic extracts were washed with water and evaporated to a white solid. The solid was covered with diethyl ether and decanted twice to give the title compound as a white solid. (0.012 g, 72%). h NMR (CDCl₃) 6 7:22-6.84 (10H, m), 6.61 (1H, s), 5.42 (1H, d), 4.693(1H; m), 4.41 (1H, d), 3.58 (1H, m), 3.45 (1H, m), 2.78-2.40 (5H, m), 1.91 (1H, m), 1.59 (2H, m), 1.41 (3H, d), 1.26 (9H, s) (rotamers observed), 0.71 (3H, d), 0.59 (3H, d); MS m/e 579.2 [M+H]+.

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25 Preparation of (2R.4S.5S.1'S)-5-(1"1-dimethyl-2-") hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1*-isopropyl-1*imidazol-2-vl)methvl-6-phenvl-2-phenvlmethvl-hexanamide

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a) 2-t-butyldimethylsiloxy-1,1-dimethylethyl-(4- 45 nitrophenyl) carbonate to care to a should be to the first of the same of the

A mixture containing bis (4-nitrophenyl) carbonate (0.996 g, 3.28 mmol); 2-t-butyldimethylsiloxy-1;1dimethylethanol (0.67 g, 1 eq) and 4-dimethylaminopyridine (0.4 g, 1 eq) in dichloromethane (50 mL) was stirred at room 35 temperature for 5 d. The mixture was diluted with dichloromethane and washed successively with H2O and saturated aqueous NaCl, and dried over Na2CO345 The solvent was removed in vacuo, and the residue was purified by flash

chromatography (silica, 20% ethyl acetate/hexanes) to afford the title compound (35%). NMR(CDCl₃) & 8.25 (2H, m), 7.35 (2H, m), 3.76 (2H, s), 1.53 (6H, s), 0.94 (9H, s), 0.09 (6H, s).

b) (2R, 4S, 5S, 1'S)-5-(2-t-butyldimethylsiloxy-1,1-dimethyl-ethoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

A solution of 2-t-butyldimethylsiloxy-1,1-dimethylethyl
4-nitrophenyl carbonate (137 mg, 0.372 mmol), (2R,4S,5S,1'S)
5-amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol
2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide (102 mg, 0.186 mmol) and DMAP (45 mg, 0.372 mmol) in methylene choride was stirred at 20°C under Ar for 24 h. The solution was washed

15 with aqueous Na₂CO₃, dried over solid Na₂CO₃ and concentrated.

Flash chromatography (4% methanol/dichloromethane) provided

the intermediate (2R,4S,5S,1'S)-5-(2-t-butyldimethylsiloxy
1,1-dimethylethoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-

dimethylethoxycarbonyl)imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide, which was dissolved in ether, washed
with 10% NaOH, dried over Na₂CO₃, and concentrated to provide
the title compound (110 mg, 78% overall). NMR(CDCl₃) δ 7.376.70 (13H, m), 6.39 (1H, d), 4.84 (1H, d), 4.55 (1H, t), 3.96
25 (1H, q), 3.69 (2H, s), 3.60-3.42 (2H, m), 2.94 (1H, s(br)),
2.85-2.44 (4H, m), 2.39 (1H, q), 1.90-1.60 (2H, m), 1.31 (6H,

d), 1.02-0.85 (18H, m), 0.83 (6H, t), 0.98 (12H, m).

(1'-isopropyl-1'-(1-(2-t-butyldimethylsiloxy-1,1-

c) (2R, 4S, 5S, 1'S)-5-(1, 1-dimethyl-2-hydroxyethoxy30 carbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2yl) methyl-6-phenyl-2-phenylmethyl-hexanamide

20 A mixture containing the compound of Example 38(b) (110
mg), and tetra-n-butylammonium fluoride (6 eq of 1M solution
in THF) under an argon atmosphere was allowed to stir at room
35 temperature overnight. The solution was diluted with
dichloromethane and washed with water, and the organic layer
was concentrated. The residue was purified by flash
chromatography (4% methanol/dichloromethane) to afford the

title compound (0.05 g, 66%). NMR (CDCl3; CD3OD) & 7.30-6.78 (12H, m), 4.42 (1H, d), 3.75-3.38 (4H, m), 2.97-2.50 (5H, m), 2.08 (1H, m), 1.70-1.56 (2H, m), 1.30 (6H, s), 0.90-0.55 (6H, dd).

Example 39

Preparation of (2R.4S.5S.1'S)-5-(1.1-dimethyl-2-hydroxy-ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide hydrochloride

A 1M solution of HCl in ether (63.5 mL) was added to a solution of the compound of Example 38(c) (35 mg, 0.064 mmol) in methanol (5 mL). The solvent was removed by rotary evaporation at 20°C, and the solid residue was triturated with ether and dried to afford the title compound as the hydrochloride salt (35 mg, 95%). NMR(CD₃OD) δ 7.37-6.85 (12H, m), 4.56 (1H, d), 3.59 (1H, m), 3.48-3.33 (3H, m), 2.85-2.48 (6H, m), 2.04 (1H, septet), 1.72-1.49 (2H, m), 1.22 (6H, d), 0.88(3H, d), 0.61 (3H, dd).

Example 40

Preparation of (2R.4S.5S.1'S)-5-(2-hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-phenylmethylhexanamide

a) benzyloxyethyl-(4-nitro)phenylcarbonate

To a solution of 2-benzyloxyethanol (2.5 g, 16.4 mmol)

and bis(4-nitrophenyl)carbonate (5.0 g, 1 eq) in

dichloromethane (200 mL), N-methylmorpholine (1.81 mL, 1 eq)

was added. The resulting mixture was allowed to stir at room

temperature for 3 d. The reaction mixture was washed

successively with H2O and saturated aqueous NaCl and dried

over Na2SO4. The solvent was removed in vacuo, and the

residue was purified by flash chromatography (silica, 20%

ethyl acetate/hexanes) to afford the title compound (4.38 g,

4.49 (2H, t), 3.70 (2H, t).

b) (2R, 48, 58, 1.8) -5-(2-henryloxy-thougher-bonyl) amino-4-t
5 butyldingthylilasy 3-[1 isopropyl-1-47-(2
benzylogy-though inidazol-2-yljasthyl-6-phenyl-2
phenylogy-though inidazol-2-yljasthyl-6-phenyl-2-

butyldisting a (1 isopropyl-1 imidazol-2-yl) methyl
10 6-phenyl-2-phenylmethyl-hexanamide (136.5 mg, 0.24 mmol) in

dichlorosichane (40 ml) under an argon strosphere,

benzylowethyl 4-nitrophenyl carbonate (150 mg, 2 eq) and 4-dimethylaminopyridine (60 mg, 2 eq) were added. The resulting mixture was allowed to stir at room temperature

overnight, and was diluted with dichloremethane. The organic extract was washed successively with agreeous Na₂CO₃, H₂O₄,

was removed in vacuo, and the residue was purified by flash chromatography (silica, 4% methanol/dichloromethane) to

20 afford the title compound (180 mg, 82%). NMR (CDCl₃) δ 7.45-6.80 (228, m), 6.62 (2H, d), 5.60 (1H, t), 5.06 (1H, d), 4.60 (2H, s), 4.52 (2H, s), 4.50 (2H, m), 4.31 (1H, m), 4.07 (2H, m), 3.80 (2H, t), 3.68 (1H, q), 3.57 (3H, q), 2.85 (1H, m), 2.77-2.41 (4H, m), 2.89 (1H, m), 1.90 (2H, m), 1.73 (1H, m),

25 0.95 (9H, s), 0.81 (6H, 6d), 0.11 (6H, d).

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c) (2R, 4S, 5S, 1 S) -5-42 kg/k-wyethoryching) amino-4-t-butyl-dimethylsiloxy 3-11 dangersyl-1 -12 2 conzyloxyethoxy-carbonyl) imidazol 2 yl) atlyl-6 phenyl 2 phenylmethyl
30 hexanamide

The compound of Example 40(b) (62 mg, 0.44 mmol) was stirred as a solution in mathemal (50 mg) with Pd(0) (10 mg) under 1 ctm hydrogen for 12 h. The mixture was filtered, the solvent was manufacture was purified by flash chromatography (silica, 44 manufacture) dichloromethane) to afford the fills compound (44 mg, 741). EMR (CDCl3) & 7.36-6.72 (122, 20, 3.23 (2H, d), 4.60 (1H, dd), 4.50-4.32 (2H,

20

25

30

m), 4.07-3.52 (5H, m), 2.96-2.32 (6H, m), 1.98-1.85 (2H, m), 0.95 (9H, s), 0.90-0.75 (6H, dd), 0.05 (6H, d).

d) (2R, 4S, 5S, 1'S) -5-(2-hydroxyethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2and the phenylmethyl-hexanamide and franch of kodownous word

To a solution of the compound of of Example 40(c) in methanol, excess aqueous HCl (approx. 5 equiv.) was added. The resulting solution was stirred at room temperature 10 overnight, and concentrated under reduced pressure. residue was diluted with H2O, and made basic with aqueous The mixture was extracted with dichloromethane, and the combined organic extracts were dried over Na2CO3. solvent was removed in vacuo, and the residue was purified by flash chromatography to afford the title compound. NMR (CD₃OD) δ 7.28-6.85 (12H, m), 4.55 (1H, d), 3.95 (1H, m), 3.73-3.40 (4H, m), 2.86-2.47 (5H, m), 1.99 (1H, m), 1.71 (1H, m), 1.22 (1H, m), 0.84 (3H, d), 0.62 (3H, d)

្ត គ្រះជីវ "ស៊ី មួយ**្តែ**ល្អភិក្សាសំខាន់។ Example 41 graph with partition

Preparation of (2R.4S.5S.1'S)-5-((1RS)-1-methyl hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

(a. 88) (1) ₹#. a) 2-t-butyldimethylsiloxy-1-methylethyl-(4-nitrophenyl)carbonate char 2Ha Carteria de la divigio de la composición del composición de la composición

A mixture containing bis (4-nitrophenyl) carbonate (3.20 g, 10.5 mmol), 2-t-butyldimethylsiloxy-1-methylethanol (2.0 g, 10.5 mmol) and 4-dimethylaminopyridine (1.30 g, 1 0.5 mmol) in dichloromethane (200 mL) was stirred at room temperature for 5 d. The mixture was then diluted with dichloromethane and washed successively with H2O and saturated aqueous NaCl and dried over Na2CO3. The solvent 35 was removed in vacuo, and the residue was purified by flash chromatography (silica, 10% ethyl acetate/hexane) to afford the title compound (88%). NMR(CDCl₃) δ 8.28 (2H, m), 7.39

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into (2H, m), 4.98 (1H, m), 3.75 (2H, d), 1.38 (3H, s), 0.92 (9H,
. Apriles (Hs), 0.11r.(6H, Ss). Respectively, year to be
                 BORN OF O IN BUY WESTERN OF
         (2R, 4S, 5S, 1'S) -5-(2-t-butyldimethylsiloxy-1-methyl-
                   ethoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-
                   1'-imidazol-2-y1) methyl-6-phenyl-2-phenylmethyl-hexanamide
                 $1 - (16) Following-the procedure of Example 38(b), except
                   substituting the compound of Example 4(a) for 2-t-
  3 6: 1; butyldimethylsiloxy-1,1-dimethylethyl-4-nitrophenyl
       $ 10 procarbonate, the title compound was prepared. NMR (CDCl3) δ
  State a as7.40-7.00 (10H/m), 6.90 (1/2H/ms), 6.72 (1/2H/ms), 6.45 (1H/ms)
       arganidd), (4.92%(1H, dd)), 4.84-4.61%(2H, m), 4.10%(1H, m), 3.76
  bracks to (1H, m), 3.58: (1H, m), 2.92-2.73: (3H, m), 2.70-2.45 (3H, m),
       1.78 (2H, m), 1.22-1.08 (3H, m), 1.04-0.81 (24H, m), 0.17-
      5 15 0.09 (12H, m)
                       this bedeem that have up and mit-
      25: 0年c)程(2R, 4S, 5S, 1'S) -5-((1RS)-1-methyl-2-hydroxyethoxycarbonyl)-
        vigs gamino-4-hydroxy-N-(1!-isopropyl-1'-imidazol-2-yl)methyl-6-
                phenyl-2-phenylmethyl-hexanamide
                             Following the procedure of Example 38(c), except using
          20
                   the compound of Example 4(b), the title compound is prepared.
                 -NMR(CD_3OD): \delta: 7.15-6.68 (12H, m), 5.72-5.60 (1H, dd), 4.58
    -ty--12--0x(1H, m);-4.38-(1H, dd);-4.06x(1H, m), 3.62 (1H, m), 3.41 (1H,
     (1H, dd), 1.92 (1H, m), 1.67 (1H, dd), 1.92 (1H, m), 1.67 (1H,
          25 m), 1.08-0.98 (3H, dd), 0.69 (3H, dd), 0.58 (3H, dd).
        The figure of the entire of the contraction of the 
       -Indian was the fellow the beautiful Example 42 for the month of
     (Come CS to the first Hilly Home to the both to the answer
         # ( Preparation of (2R.4S.5S.1'S)-5-(2-hydroxy-1-#25 )
      ad30 .cyclopentyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-
         badesimidazol-2-vl)methyl-6-phenyl-2-phenylmethylhexanamide
         has the limited attemptioned with on any or the lander of the
               65a): (trans) -2-(t-butyldimethysiloxy) -cyclopentanol: 5
     cubices off To a mixture of t-butyldimethylsilyl chloride (5.08 g,
                   33.7 mmol) and imidazole (2.30 g, 33.7 mmol) in DMF (10 mL),
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35 33.7 mmol) and imidazole (2.30 g, 33.7 mmol) in DMF (10 mL), as a solution of trans-1,2-cyclopentanediol in DMF (4 mL) was added. The reaction mixture was stirred overnight at 25°C.

The reaction mixture was diluted with ice water and extracted

.

with ether. The ether extract was washed with water and brine, dried over magnesium sulfate; filtered and the solvent removed in vacuo. The residue was purified by flash chromatography (silica; 9:1 hexane:ethyleacetate) to the title compound as an oil (3.44 g; 49%) modisography 2

b) ((trans)-2-(t-butyldimethysiloxy)-cyclopentyl)-(4-nitrophenyl) carbonate

To a solution of the compound of Example 42(a) (1.08 g, 5 mmol) and DMAP (0.611 g, 5 mmol) in dichloromethane (12 mL), bis (4-nitrophenyl) carbonate (1.52 g, 5 mmol) was added. The solution was stirred overnight at 25°C. The reaction mixture was diluted with dichloromethane (15 mL), and washed with water and brine. The organic extract was dried over magnesium sulfate, filtered, and the solvent was removed at reduced pressure. The residue was triturated with hexane:ethyl acetate (1:1) and filtered. The filtrate was evaporated to an oil and purified by flash chromatography (silica, 9:1 hexane:ethyl acetate) to yield the title compound as an oil (1.75 g, 92%).

c) 5-((trans)-2-t-butyldimethylsiloxy-cyclopentyloxy-carbonyl) amino-4-t-butyldimethysiloxy-N-[1'-isopropyl-1'-(1-(2-t-butyldimethysiloxy-cyclopentyloxycarbonyl)) imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide().

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A solution of 5-amino-4-t-butyldimethylsiloxy-N-[1'isopropyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethylhexanamide (171 mg, 0.311 mmol), DMAP (76.1 mg, 0.623 mmol)
and the compound of Example 42(b) (238 mg, 0.623 mmol) in
dichloromethane (9 mL) was stirredtovernight at 25°C. The
reaction mixture was diluted with dichloromethane, washed
with water and saturated sodium bicarbonate solution, and
dried with magnesium sulfate. The organic extract was
filtered and the solvent was removed in vacuo. The residue
was purified by flash chromatography (silica, 4:1
hexane:ethyl acetate) to yield the title compound as an oil
(150 mg, 47%).

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d) 5-((trans)-2-hydroxy-cyclopentyloxycarbonyl) amino-4hydroxy-N-[1'-isopropyl-1'-imidazol-2-yl]methyl-6-phenyl-2phenylmethyl-hexanamide

To a solution of the compound of Example 42(c) (150 mg, 0.145 mmol) in methanol (5 mL), 3N HCl (3 mL) was added. The solution was stirred overnight at 25°C. The methanol was evaporated in vacuo, and the residue was diluted with water and extracted with ether. The aqueous solution was neutralized with 5% sodium carbonate (~pH 7) and a solid precipitated. The solid was filtered, washed with water and dried in vacuo to yield the title compound (51.5 mg, 63%).

NMR(CD3OD, 400 MHz), 8,7.0-7.3 (m, 10H), 6.87 (s, 2H), 4.63 (m, 2H), 3.88 (m, 1H), 3.55 (d, 1H), 2.5-2.9 m, 5H), 1.4-2.1 (br, 9H), 0.88 (d, 3H), 0.71 (d, 3H); TLC Rf 0.27 (silica, 8% methanol/chloroform).

ba granestill die to by aldern a b Example 43 mag tagge of its

Street at the insulation of

20 hydroxy-N-(1'-isopropyl-1'-imidazol-2-v1)methyl-6-phenyl-2-phenylmethylhexanamide

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-13) Furturative in calcas (In consider a could be 15) in the 15 feet of 17.

manife with the later of the Children W.

(b) 4-t-butyldimethylsiloxy-butanoic acid (c) (c) (a) (5.0 g) was addissolved in acetic acid: tetrahydrofuran: water (2:2:1, 50 mL)

70. (111 L) 30. 5 (400 c) 80.7 (400 cm 6.7-6.7 (30) m

solution and stirred for 2.5 h. The solution was diluted with water and extracted with ether. The ether solution was

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dried with magnesium sulfate, filtered and evaporated to an oil. The oil was purified by flash chromatography (silica, hexane-ethyl acetate, 9:1) to yield the title compound as an oil (180 mg).

butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl6-phenyl-2-phenylmethyl-hexanamide (175 mg, 0.319 mmol), 4-tbutyldimethylsiloxy-butanoic acid (84 mg, 0.41 mmol), BOP
reagent (148, 0.335 mmol), triethylamine (46 µL, 0;335 mmol)
and dichloromethane (4 mL) were stirred at 20°C under Ar for

24 h. The reaction mixture was diluted with dichloromethane,
washed with aqueous Na₂CO₃, water and brine, and dried over
solid magnesium sulfate. The organic phase was filtered, and
concentrated in vacuo. The residue was purified by flash
chromatography (silica, 2% methanol/chloroform) to provide
the title compound.

d) (2R,4S,5S,1'S)-5-(4-hydroxybutanoyl)amino-4-hydroxy-N-(1',... isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-36-36
phenylmethylhexanamide

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A solution of the compound of Example 43(c) (177 mg, 0.236 mmol) and tetra-n-butylammonium fluoride: (2.84 mL, 2.84 mmol, 1M solution in THF) was stirred under an argon atmosphere at room temperature overnights. The solution was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution, and water, and the organic layer was concentrated. The residue was precipitated from the ethyl acetate solution to afford the title compound. NMR δ (CD30D, 400 MHz) 7.0-7.3 (m, 10H), 6.86 (s, 2H), 4.62 (d, 1H), 4.05 (m, 1H), 3.43 (t, 2H), 2.55-2.90 (m, 4H), 2.60 (m, 1H), 2.17 (m, 2H), 2.05 (m, 1H), 1.76 (m, 1H), 1.67 (m, 2H), 1.55 (m, 1H), .88 (d, 3H), .72 (d, 3H); TLC R_f 0.40 (silica, 10% methanol/chloroform).

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Example 44

Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(benzyloxycarbonyl) valylamino-6-phenyl-N-(1'-isobutyl-1'-

- 5 imidazo-2-vl)methyl-hexanamide
- (a) (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-butyldimethylsiloxy-5-(benzyloxycarbonyl) valylamino-6-phenyl-N-(1'-isobutyl-1'-(imidazo-2-yl)) methyl-hexanamide.
- A solution of carbobenzyloxy-(L)-valine (50.4 mg, 0.20 and figuremmol), the product of Example 13(a) (110 mg, 0.20 mmol), BOP startreagent (88.7 mg, 0.20 mmol) and triethylamine (28 µl, 0.20 mmol) in methylene chloride (4 mL) was stirred at 25°C for 4 d. The reaction mixture was diluted with methylene chloride,
- washed with saturated sodium bicarbonate and the organic layer was concentrated. The product was purified by flash chromatography (silica gel, 4% CH2Cl2/ MeOH) to give the state at title compound (104 mg, 67%).
- (b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(benzyloxycarbonyl-valyl) amino-6-phenyl-N-(1'-isobutyl-1'imidazo-2-yl) methyl-hexanamide.

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To a solution of the compound of Example 44(a) (104 mg, 0.133 mmol) in MeOH (8 mL), 3N HCl (2 mL) was added. The

- 25 °C. The methanol was removed at reduced pressure and 10% sodium carbonate was (%) added to pH ~7.5. Ether (10 mL) was added and the solid
- The bias product was: filtered and dried in vacuo to provide the title $t_{\rm con}$ [recompound (58 mg, 65%). NMR(CDCl3) $\delta_{\rm c}$ 0.62%(d, 3H), 0.78 (d,
- ite 3013 3H), 0.82 (d, 3H), 0.90 (d, 3H), 1.62 (m, 2H), 1.96 (m, 1H),
 - $\texttt{seff} \quad \textbf{2.06} \quad (\texttt{m, v1H}) \,, \, \textbf{2.55} \,, \, (\texttt{m, 1H}) \,, \, \, \textbf{2.77} \,, \, (\texttt{m, 4H}) \,, \, \, \textbf{3.38} \,, \, (\texttt{s, 1H}) \,, \, \, \textbf{3.53}$

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- but you (m, 11H) / 3.91 (M, 1H) / 3.99 (m, 1H) / 4.47 (d, 1H) / 5.11 (s,
- ((22V) 2H), 5.78 (d, 红H), 6.85 (s, 2H), 6.92-7.34 (m, 15H);

. (19**35**) (1.1) (1.1) (1.1) (1.1) (2.1) (1.1) (

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Example 45

Preparation of (2R,4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(Nacetylvalyl) amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2yl) methyl-hexanamide the asset the grant of the second the second

(a) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-t-butŷldimethylsil) oxy-5-(N-acetyl-valyl) amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2yl) methyl-hexanamide of a conference of the State State of the

To a solution of N-acetyl-(L)-valine: (40.3 mg, 0.253 mmol) in dry THF (8 mL) at -40°C was added n-methylmorpholine : (55.7 µl, 0.506 mmol) followed by isobutyl; chloroformate (33.5 μl, 0.253 mmol). The reaction mixture was stirred for 15 min, and the compound of Example 13(b) (139 mg, 0.253 mmol) in THF (3 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 d. reaction was diluted with ethyl acetate, and washed with water and brine. The organic solution was dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (silica, 4% methanol/chloroform) to give the product as an . . . oil (47 mg, 27%).

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(b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(N-) 25 acetylvalyl) amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2yl) methyl-hexanamide. Be to be error to all box as has an a

To a solution of the compound of Example: 45(a): (47 mg, 0.0681 mmol) in methanol (3 mL), 3N HCl (0.5 mL) was added. The reaction was stirred for 16th at 25°C. The methanol was 30 removed under reduced pressure and the solution was diluted with water and neutralized with 5% sodium carbonate. The solid product was filtered, washed with water and ether, and dried in vacuo to yield the title compound (29.5 mg, (75%). NMR (CD3OD) δ 0.70 (d, 3H), 0:88 (m, 9H), 1.57 (m, 1H), 1.70 (m, 1H), 1.92 (s, 3H), 2.05 (m, 1H), 2.55 (q, 1H), 2.77 (m, 4H), 3.57 (d, 1H), 4.03 (m, 2H), 4.60 (d, 1H), 6.87 (s, 2H), 6.95-6.20 (m, 10H); MS m/e 575 [M+H]+.

Forms of well to see how the order to be Example 46.

Preparation of (2R,48,5S,1'S)-5-[(imidazol-2-

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- y1) methyloxycarbonyllamino-4-hydroxy-N-(1'-isopropyl-1'-
- 5 5 imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide
- im Section a) (1-(benzyloxymethyl) imidazol-2-yl) methyl-(4-0)
- 20.0 (6 nitrophenyl) carbonate(6) 40.0 Color of Color of Color
- A mixture of bis(4-nitrophenyl) carbonate, (1-
 - 10 benzyloxymethyl)imidazol-2-yl)methanol and 4-

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- dimethylaminopyridine was reacted according to the procedure
 - -Paramof Example 14(a) to afford the title compound (58%).
 - NMR (CDC1₃, 400 MHz) δ 8.18 (d, 2 H, J=8.38 Hz), 7.44-7.23 (m,
 - 380 () 7H), 7.11 (s, 1H), 7.13 (s, 1H), 5.48 (s, 2H), 5.44 (s, 2H),
 - 077: 15 74.49 (8,92H) 1885 Calland From Color Co
 - (1-benzyloxymethyl)imidazol-2-
 - ne hyloxycarbonyl) amino-4-t-butyldimethylsiloxy-N-(1'-
 - or isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
 - . "20 hexanamide" case is a different for Spaceto and distance
 - on A mixture of the compound of Example (46(a), 17)
- (085 (m) 2 (2R, 48) 55, 1'S) -5-amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-
- 53 :: (GEZ-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide, and 4-
- dimethylaminopyridine was reacted according to the procedure
 - 25 of Example 14(b) to afford the title compound (32%).
 - NMR(CDCl₃) & 7.50-6.60 (m, 19H), 5.25 (m, 2H), 5.11 (d, 2H,
 - J=11.03 Hz), 4.68 (m, 1H), 4.39 (m, 2H), 3.97 (m, 1H), 3.67
 - (m, 1H), 2.88 (m, 1H), 2.72-2.28 (m, 6H), 1.85 (m, 1H), 1.60
- (m, 15H), (m, 1H), (0.92-0.81) (m, 15H), (0.80) (s, 3H), (0.06) (s, 3H);

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- c) (2R, 4S, 5S, 1'S)-5-(imidazoyl-2-yl-methyloxycarbonyl)amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
- -1) 351- hexanamide oction (Aynorf ord); (4) 513 15 (428818)
 - The compound of Example 46(b) (58 mg, 0.073 mmol);
- problems methanol (30mL), and 10% Pd on carbon (50 mg) were combined
- and stirred under 1 atm of H2 for 24 h. Additional catalyst

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(50 mg) was added and stirring under H₂ was continued for 8
h. The reaction was filtered through Celite®, concentrated and flash chromatographed (silica, step/gradient, 0-8% MeOH/CH₂Cl₂) to yield the title compound (28 mg/, 57%).
5 NMR(CDCl₃) δ 7.29-6:83 (m, 14H); 5.05 (d, 1H, J=11.2 Hz),
4.91 (d, 1H, J=11.2 Hz), 4.71 (m, 1H), 3.92 (m, 1H), 3.61 (m, 1H), 3.02 (m, 1H), 2.81-2:54 (m, 4H), 22:36 (m, 1H), 1.93 (m, 1H)

(d, 3H, J=7.1 Hz), 0.84-0.05; (m, 6H); MS(ES)/m/e 673 [M+H]+.

d) (2R,4S,5S,1'S)-5-(imidazol-2-yl-methyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide 8 1 4 4 (2001) 6 (2001) 6 (2001)

1H), 1.59 (m, 1H), 0.91 (d, 3H, J=7.1 Hz), 0.89 (s, 9), 0.69

The compound of Example 46(c): (24 mg, 0.035 mmoL), 95% aqueous EtOH (0.50 mL), and concentrated aqueous HCl (0.050 mL) were stirred at 23°C for 24 h. The solution was diluted with H2O (5 mL) washed with EtOAc and then the aqueous phase was made basic by addition of solid K2CO3. (Extraction with EtOAc, concentration of the organic extract and trituration with CH2Cl2 afforded the title compound (14 mg, 72%). NMR (CDCl3) δ 7.33-6.85 (m, 14H), 5.11 (d, 1H, J=10.8 Hz), 4.96 (d, 1H, J=10.8 Hz), 4.47 (m, 1H), 3.72 (m, 1H), 3.38 (m, 1H), 2.81 (m, 4H), 2.59 (m, 1H), 2.07 (m, 1H), 1.72 (m, 1H), 1.62 (m, 1H), 0.78 (d, 3H, J=6.63 Hz), 0.67 (d, 3H, J=6.63 Hz); (m, 6H); MS(ES) m/e 559 [M+H]⁺.

Example 47 . A (cut 20, 20 3

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Preparation of (2R.4S.5S.1'S.1"RS)-5-((1"-(imidazol-2-yl)-2"methyl)propyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

a) (1RS)-1-((1-benzyloxymethylimidazol-2-yl)-2-(3 a) methyl)propyl-(4-nitrophenyl)carbonate-11-1799-38-3

. . .

A mixture of bis(4-nitrophenyl) carbonate, (1RS)-1-((1-benzyloxymethylimidazol-2-yl)-2-methyl) propanol and 4-dimethylaminopyridine was reacted according to the procedure of Example 14(a) to afford the title compound (61%). NMR

(CDCl₃) δ 8.18 (d, 2H, J=8.31 Hz), 7.38-7.21 (m, 7H), 7.13 (s, 1H), 6.94 (s, 1H), 5.74 (d, 1H, J=11.1 Hz), 5.47 (d, 1H, J=10.2 Hz), 5.28 (d, 1H, J=10.2 Hz), 4.53 (d, 1H, J=11.3 Hz), 4.41 (d, 1H, J=11.3 Hz), 2.64 (m, 1H), 1.18 (d, 3H, J=6.02 Hz), 0.87 (d, 3H, J=6.02 Hz); MS(ES) m/e 426 [M+H]⁺.

b) (2R, 4S, 5S, 1'S, 1"RS) -5-((1"-(1-benzyloxymethylimidazol-2-ye yl)-2"-methyl-propyl) oxycarbonyl) amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-(1-(1"-(1-

10 benzyloxymethylimidazol-2-yl)-2"-

bestalid methylpropyl)oxycarbonyl)imidazol-2-yl)methyl-6-phenyl-2-besphenylmethyl-hexanamide?

43 give 30 dalk Almixture of the compound of Example 47(a) (145 mg, 0.33

mmol), the compound of Example 13(a) (75.9 mg, 0.14 mmol), 475.5 dimethylaminopyridine (41 mg, 0.33 mmol) and DMF (0.5 mL) was
stirred under argon for 18 h. The DMF was evaporated in
vacuo and the residue was combined with 10% aq K2CO3 (10 mL)
and extracted with EtOAc. The combined extracts were washed
with saturated aq NaHCO3, dried (K2CO3), filtered and

- 20 concentrated in vacuo. The residue was flash chromatographed = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 1.001 (silica, step
- imidazol-2-yl)-2"-methyl-propyl)oxycarbonyl]amino-4-hydroxy-

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for the back solution of the compound of Example 47(b): (81 mg, 0.07 for disemble), CH3OH (0.75 mL), and 3N aqueous HCl (0.25 mL) was discretized at 23°C for 20 h. The reaction mixture was diluted with H2O (10 mL), and washed with EtOAc (3 x 15mL). Solid 5 350 K2CO3, was added to give a basic solution (pH>12), which was extracted with EtOAc. The extracts were dried (K2CO3),

in filtered, concentrated and flash chromatographed (silica, to give the title compound

(34.9 mg, 65%). ¹H NMR (CDCl₃) δ 7.43-6.79 (m, 9H), 5.87, 5.66 (2d, 1H, J=10.66, 10.85 Hz), 5.28 (m, 2H), 4:68 (m, 1H), 4.42 (m, 2H), 3.71 (m, 1H), 3.58 (m, 1H), 2.90-2.31 (m, 6H), 36 - 2.11 (m, 1H), 1.75, 1.51 (2m, 2H), 1.05, 0.97 (2d, 3H, 5 J=6.32,6.45), 0.68 (m, 9H). 3 det, 190 (190-3)

d) (2R, 4S, 5S, 1'S, 1"RS) -5-((1"-(imidazol-2-yl)-2"-..... methyl)propyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl) methyl-6-phenyl-2-phenýlméthyl-hexanamide.

A mixture of the compound of Example 47(c) 434 mg; 0.047 mmol), CH3OH (4 mL), and 10% Pd/C((34 mg), was stirred under H2 (1 atm) for 26 h. The suspension was filtered 100 m through Celite®, concentrated, and triturated with CH2Cl2 to δ yield the title compound (4 mg, 14%). HNMR3 (CDCl3/CD3OD) δ 15 7.7.32-6.71 (m, 14H), 5.38 (m, 1H), 4.55 (m, 1H), 143:72 (m, 1H), 3.55 (m, 1H), 2.78 (m, 4H), 2.55 (m, 1H), 2.15 (m, 2H), 1.60 (m, 2H), 1.03-0.61 (m, 12H). Har well help twomy

Example 48 to the state of the

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-(imidazoI-2-y1)imidazol-2v1) lmethv1-6-phenv1-2-phenvlmethv1-hexanamide ()

(a) (1'S)-1'-(carbobenzyloxy)amino-1'-isopropyl-1'-(4- as 25 (imidazol-2-yl) imidazol-2-yl) methane

Cbz-(L)-valinal (0.45 g, 1:4 mmol) was stirred in anhydrous methanol at 0°C under argon. Glyoxal (40% in water) (0.22 mL, 1.4 mmol) and ammonium hydroxide (29% NH3) (0.88 mL, 14 mmol) were added and the mixture was allowed to stir at 0°C for 1 h. The cooling bath was removed and the solution stirred at room temperature for 16 h. The methanol was evaporated in vacuo and the residue was diluted with 5% aqueous HCl. After extracting with dichloromethane, the aqueous layer was made basic with solid sodium carbonate and extracted with dichloromethane. The combined organic extracts were dried over sodium carbonate, filtered, and evaporated to a solid which was chromatographed (silica, 4%

methanol/dichloromethane) to give the title compound (0.216 g, 43%) as a white solid. NMR (CDCl3) δ 7.15 (6H, s(br)), 6.88 (2H, s), 6.30 (1H, d), 4.89 (2H, dd), 4.52 (1H, t), 2.05 (1H, m), 0.73 (3H, d), 0.62 (3H, d). MS m/e 340.2 [M+H]⁺

(b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N[1'-isopropyl-1'-(4-(imidazol-2-yl) imidazol-2-yl)] methyl-6phenyl-2-phenylmethyl-hexanamide

The compound of Example 48(a) (0.13 gm.) was dissolved
in anhydrous methanol with 10% Pd on activated carbon (0.02
g). Hydrogen gas was bubbled through the solution via
balloon for 1 h and the solution was stirred overnight under
a hydrogen atmosphere. The mixture was filtered through a
pad of Celite® and evaporated to yield 1*-amino-1*-isopropyl15 [4-(imidazol-2-yl)imidazol-2-yl]methane as a white solid
(0.13 g, 100%).

This compound was combined with the compound of Example 13(a) (0.334 g, 0.63 mmol), BOP reagent (0.28 g, 0.63 mmol), and triethylamine (0.13 mL, 0.945 mmol) in DMF (1 mL) and allowed to stir under Ar for 3 d. The DMF was evaporated in vacuo and the residue was diluted with dichloromethane. The solution was washed with water and brine. The organic layer was dried over sodium carbonate, filtered, and evaporated to yield (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethysiloxy-N-[1'-isopropyl-1'-(4-(imidazol-2-yl) imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl hexanamide as

A portion of the solid (0.100 g, 0.14 mmol) was stirred in THF at room temperature under argon. Tetrabutylammonium fluoride; (0.84 mL, 0.84 mmol) was added and the mixture was allowed to stir for 16 h. The solution was diluted with water and extracted twice with dichloromethane. The combined organic extracts were washed with water and evaporated to an oily residue. The residue was dissolved in THF and several 35, drops of diethyl ether were added until a white precipitate formed. The precipitate was collected by filtration and dried in vacuo to yield the title compound as a white solid (76 mg, 90%). NMR (CD3OD) & 7.37-6.84 (13H, m), 4.61 (1H,

d), 3.69 (2H, m), 3.54 (1H, d), 2.84-2.52 (5H, m), 2.06 (1H, m), 1'.83 (2H, m), 1.57 (1H, m), 1.30 (9H, s), 0.87 (3H, d), 0.69 (3H, d); MS m/e 601.2 [M+H]+

Example 49

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Preparation of (2R;4S;5S;1'S)-5-[di(hydroxymethyl)methoxycarbonyllamino-4-hydroxy-N-(1'-isopropyl-1'-imidazol2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

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a) di(t-butyldimethylsiloxymethyl) methyl-(4-nitrophenyl)
carbonate

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A mixture containing bis (4-nitrophenyl) carbonate (1.89 g, 6.21 mmol), di(t-butyldimethylsiloxymethyl) methanol (2.00 g, 1 eq) and 4-dimethylaminopyridine (757 mg, 1 eq) in dichloromethane (100 mL) was stirred at room temperature for 2 d. The mixture was diluted with dichloromethane and washed with saturated aqueous Na₂CO₃, brine, and dried over Na₂SO₄.

The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 10% ethylis

- 20 purified by flash chromatography (silica, 310% ethyl 5 compound (75%). NMR (CDCl₃) δ 8.29 (2H, m), 7.37 (2H, m), 3,96 (1H, m), 3.85 (2H, d), 3.82 (2H, d), 0.89 (18H, s) (0.09° (12H, s).
- 25 b) (2R,4S,5S,1'S)-5-(di(t-butyldimethylsiloxymethyl)methyloxycarbonyl]amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

A solution of di(t-butyldimethylsiloxymethyl) -methyl 430 nitrophenyl carbonate (475 mg, 0.974 mmol), the compound of
Example 13(a) (178 mg, 0.325 mmol) and dimethylaminopyridine
(119 mg, 0.974 mmol) in methylene choride was stirred at 20°C
under Ar for 24 h. The solution was washed with aqueous
Na₂CO₃, dried over solid Na₂CO₃ and concentrated in vacuo.

35 Flash chromatography (silica; 4% methanol/dichloromethane) of the residue provided the intermediate (2R,4\$,5\$,1'\$)-5-(di(t-butyldimethylsiloxymethyl) methyloxycarbonyl) amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-(1-(di(t-

butyldimethylsiloxymethyl) methyloxycarbonyl) imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide, which was dissolved in ether, washed with 10% NaOH, dried over Na₂CO₃, and concentrated to provide the title compound (197 mg, 71%).

5 NMR (CDCl₃) & 7.43-7.05 (10H, m), 6.90 (2H, s), 6.65 (1H, bs), 5.09 (1H, d), 4.78 (1H, bd), 4.08 (1H, m), 3.89-3.50 (7H,m) 3.00-2.80 (4H, m), 2.65 (1H, m), 2.55-(2H, m), 1.90 (1H, m), 1.78 (1H, m), 1.10-0.85 (33H, m), 0.20-0.06 (18H, m), 2.55 (1H, m), 2.55 (1H

(4) 10x 0.00 (40) (40) (40) (40) (50) (50) (50) (50) (50) (50) (50)

c) (2R, 4S, 5S, 1'S) -5- (di (hydroxymethyl) methoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2phenylmethyl-hexanamide

A mixture containing the compound of Example 49(b) (50 mg) and ethereal HCl (4 eq) was allowed to stir in methanol:water (9:1) at room temperature overnight. The solvent was removed in vacuo, and the residue was diluted with ethyl acetate and washed with saturated aqueous Na₂CO₃. The product was purified by flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (29 mg, 94%). NMR (CD₃OD) δ 7.20-6.80 (10H, m), 6.71 (2H, s), -4.50 (1H, d), 3.90 (1H, m), 3.65-3.34 (5H, m), 2.82-2.45 (6H, m), 1.99 (1H, m), 1.74 (1H, m), 1.52 (1H, m), 0.78 (3H, d), 0.60 (3H, d).

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Example 50

Preparation of (2R.4S.5S.1'S)-5-(1-oxo-thian-4-)
yl)oxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-230, yl)methyl-6-phenyl-2-phenylmethylhexanamide

Bridge 3: 3 Reacting the compound of Example 32(b) (81 mg, .133mmol)

E with m-chloro perbenzoic acid (23 mg, 0.133mmol)in CH2Cl2
yielded the title compound. NMR (CD3OD) & 7.20-6.85 (10H,

m), 6.78 (2H, s), 4.51 (1H, d), 3.66 (1H, m), 3.42(1H, m),
35H 2.95-2.41 (9H, m), 2.32-2.01 (2H, m), 1.99-1.63 (4H, m),

(335H 2.95-2.41 (2H, m), 0.78 (3H, d), 0.60 (3H, d); MS m/e 595.2
[M+H]+.

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Preparation of (2R.4S.5S.1 S)-5-((tetrahydrosulfonylpyran-4vl)oxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2v1) methyl-6-phenyl-2-phenylmethylhexanamide 303) # 10 2

Reacting the compound of Example 50; (31 mg, 49.2 mol) with m-chloro perbenzoic acid (10 mg, 59.2 mmol), in methylene chloride yielded the title compound. NMR (CD3OD) δ. 7.20-6.85 (10H, m), 6.76 (2H, s), 4.48 (1H, d), 3.68 (1H, m), 3.44(1H, m), 2.96-2.42 (9H, m), 2.32-2.04 (2H, m), 1.97-1.62 (4H, m), 1.61-1.43 (2H, m), 0.79(3H, d), 0.60 (3H, d); MS m/e 611.2 the transfer of the transfer of the transfer of

Example 52 to the first to

Preparation of (2R.4S.5S.1'S)-5-(1.1-dimethyl-2-idamet acetoxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropylimidazol-2-vl)methyl-6-phenyl-2-phenylmethyl-hexanamide

2012 (a) 0.(2R,4S,5S,1'S)-5-(1,1-dimethyl-2-) abolic mailtan hydroxyethoxycarbonyl)amino-4-(t-butyldimethylsilyl)oxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

The compound of Example 38(b) (223 mg, 0.221 mmol) was dissolved in 10% aqueous methanol and combined with 1M HCl in ether (0.221 mL, 1 eq) at room temperature. After completion of the reaction the solvents were removed in vacuo. residue was dissolved in dichloromethane and washed with aqueous saturated Na2CO3. The organic layer was concentrated and the residue was purified by flash chromatography (silica, 1 4% methanol/dichloromethane) to provide the title compound (138 mg, 94%). NMR (CDCl3) 8-7.38-6.81 (12H; m) /4.93 + 4.65 (1H, d, rotamers), 4.81+ 4.48 (1H, t, rotamers), 4.15 + 4.08 (1H,d, rotamers), 3.90 (1H,q), 3'.72 (2H, m), 3.50+3'.38 (1H, 35 d, rotamers); 2.98-2.48 (5H, m); 2.35 (1H, m); 1.98 (1H; m), 1.79 (1H, m); 1.60 ((1H, m); 1.30 ((3h; s); 1.29 (3H,s), 1.09 -0.85 (15H, m), 0.79 (3H, d), 0.11 (6H, m).

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(m) medacetoxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-. ved .: [imidazol-2-yl] methyl-6-phenyl-2-phenylmethyl-hexanamide

is the compound of Example 52(a) (103 mg, 0.155 mmol) was

Will 5 stirred with acetic anhydride (30 mg, 0.309 mmol) and DMAP (40 mg, 0.309 mmol) in methylene chloride at room temperature

, i.e. under argon overnight. The solvent was removed in vacuo and

the residue was flash chomatagraphed (silica, 4% methanol/dichloromethane).

The resulting 4-t-butyldimethylsiloxy intermediate (105) mg, 0.140 mmol) was stirred in methanol:water (9:1) with 1M HCl in ether (0.14 mL, 1 eq). The solvents were removed in solution was washed with aqueous Na2CO3. The organic layer

1315 was concentrated and the residue was purified by flash

chromatography (silica, 5% methanol/dichloromethane) to

 $_{\rm eff}$ $_{\rm eff}$ provide the title compound (82 mg, 91%). NMR (CD3OD) δ 7.29-

6.90 (10H, m), 6.81 (2H, s), 4.51 (1H, d), 4.05 (2H, s), 3.59(1H, m)/53.42 (1H, m), 2.80-2.45 (5H, m), 2.00 (1H, m),

(b) 2088; 1198 (3H, s), 1.72 (1H, m), 1.50 (1H, m), 1.34 (6H, d) 0.81

(m 30 (3H, d), 0.60 (3H, d). 3 5 5 5 5 5

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Example 53

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- Preparation of (2R.4S.5S.1'S)-5-((1.1-dimethyl-2-(benzyloxycarbonylglycyloxy)ethoxycarbonyl)amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide hydrochloride salt
- 30 a) (2R, 4S, 5S, 1'S) -5-((1, 1-dimethyl-2carbobenzyloxyglycyloxy) ethoxycarbonyl) amino-4-(tbutyldimethylsilyloxy)-N-(1'-isopropyl-1'-imidazol-2-Way o([y1] methyl-6-phenyl-2-phenylmethyl-hexanamide

The compound of Example 52(a) (100 mg, 0.151 mmol) was reacted with 2-chloro-1-methyl-pyridium iodide (92 mg, 0.36

cay (mmol); DMAP (75 mg, 0.60 mmol) and Cbz-glycine (63 mg, 0.30 mmol) in methylene chloride (5 mL) under argon at reflux for 183 h. Solvents were removed in vacuo and the product was

purified by flash chromatagraphy (silica 480) (6) methanol/dichloromethane) nto provide the title compound (95 1 : mg, 73%). NMR (CDCl3) δ.7.41-6.471(1/H_{ft} m) / 26.62_{ft} (1H, bs), - 110 6.00 (1H,m), 5.20 (1H, m), 5.15 (2H, us), 04.830+ 4.55 (1H, d, 5 rotamers), 4.65+4.48 (1H, Et, Erotamers), E4v81v+24.38 (1H, q, rotamers), 4.03 (1H,q), 4.02 (2H, d), 3:85+3.68 (2H, d, rotamers), 2.85-2.48 (5H, m), 2.38 (1H, m); 1.905(1H, m), 1.55 (1H, m), 1.38 (3h, s), 1.29 (3H,s), 0.90 e(9H, m), 0.85 (3H, d), 0.70 (3H, d), 0.11 (6H; m) per dole \ long dries and the control of predicate off.

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e_ (1.1. b) (2R,4S,5S,1'S)-5-((1,1-dimethyl-2-(元)) (1,0 人)) (benzyloxycarbonyl)ethoxycarbonyl)amino-4-hydroxy-N-(1"isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylthexanamide hydrochloride salt divinities and solution

The compound of Example 53(a) (12 mg, 0.014 mmol) was stirred in methanol:water (9:1) with 1M'HCl (2) eq) in ether The solvents were removed in vacuo to give the overnight. title compound (8 mg, 73%). NMR(CD3OD) (8 7.35) (2H,s), 7.31-6.85 (15H, m), 5.00 (2H, s), 4.59 (1H, d), 4.15; (1H, Ed, re = 20 : rotamers), 4.65+ 4.48(1H, t, rotamers), 4.81 + 4.38 (2H, dd),

3.80 (2H,d), 3.59 (1H, m), 3.40 (1H, d); 2.85-2.48 (5H, m), 2.00 (1H, m), 1.60 (1H, m), 1.55 (1H, m), 1.31 (3h, s), 1.29 (3H,s), 0.91 (3H, d), 0.60 (3H, d),

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Preparation of (2R.4S.5S.1'S)-5-((1.1-dimethy)-2-021 glycyloxy)ethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-vl)methyl-6-phenyl-2-phenylmethyl-hexanamide dihydrochloride salt A Property of the State of the

a) (2R, 4S, 5S, 1'S)-5-(1, 1-dimethyl-2-11. 1) #6-45-19. do. glycyloxyethoxycarbonyl) amino-4-(t-butyldimethylsilyl) oxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide | Property of Mana-Najizha (hariyaya)

The compound of Example 53(a) (58)mg, (6.0678mmol) was stirred in methanol with 10% Pd/C (50. mg), under 1 atm hydrogen overnight. The reaction mixture was filtered

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through Celite® and the solvents were removed in vacuo to yield the title compound (48 mg, 98%). NMR(CD3OD) δ 7.32-7.02 (10H, m), 6.99 (2H, s), 4.68 (1H, d), 4.40-4.28 (2H, dd), 3.81 (2H, d), 3.80-3.67 (2H, m), 2.90-2.49 (5H, m), 2.15 (1H, m), 5 1.97 (1H, m), 1.48 (1H, m), 1.40 (3H, s), 1.39 (3H,s), 1.15 (3H, d), 0.95 (9H, s), 0.70 (3H, d), 0.11 (6H, d).

b): (2R, 4S, 5S, 1'S)-5-((1, 1-dimethyl-2-glycyloxy) ethoxy-carbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide dihydrochloride salt

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The compound of Example 54(a) (43.5 mg, 0.060 mmol) was stirred in methanol:water (9:1) with 1M HCl in ether (0:12 mL, 2 eq) for 2 d. The solvents were removed in vacuo and the product was trituated with ether:methanol (20:1) to yield the title compound (40 mg, 98%). NMR(CD3OD) & 7.35 (2H, s), 7.30-6.92 (10H, m), 4.60 (1H, d), 4.25 (2H, dd), 3.75 (2H, d), 3.59 (1H, m), 3.49 (1H, m), 2.90-2.51 (6H, m), 2.10 (1H, m), 1.65 (1H, m), 1.54 (1H, m), 1.30 (6H, s), 0.90 (3H, d), 0.60 (3H, d).

Example 55

- 25 hydroxylethoxycarbonyllamino-4-hydroxy-N-(1'-isopropyl-1'-(4
 - isopropylcarbonylimidazol-2-yl))methyl-6-phenyl-2phenylmethyl-hexanamide dihydrochloride salt
 - a) (2R,4S,5S,1'S)-5-amino-4-t-butyldimethylsiloxy-N-[1'-
 - 30 isopropyl-1'-(4-isopropylcarbonyl-imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide
 - Using the procedure of Example 13(a), except substituting the compound of Example 28(d), the title compound was prepared.
- hydroxy) ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(4-

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isopropylcarbonylimidazol-2-yl))methyl-6-phenyl-2-:
phenylmethyl-hexanamide dihydrochloride salt

Following the procedures of Example 38 (b) -38 (c), except substituting the compound of Example 55 (a). for (Ε.) 5. (2R, 4S, 5S, 1'S) -5-amino-4-t-butyldimethylsiloxy-N-('- isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide, the title compound was prepared. NMR (CDCl3) δ 7.49 (1H, s), 7.13 (5H, m), 6.84 (5H, m); 5.53 (1H, d), 4.47 (1H, d), 3.79 (1H, m), 3.60 (1H, m), 3.44 (2H, m), 3.16 (1H, m), 2.81-2.50 (5H, m), 1.92 (1H, m), 1.62 (2H, m), 1.18 (14H, m), 0.72 (3H, d), 0.58 (3H, d); MS m/e 621.4 [M+H]+.

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Preparation of (2R,4S,5S,1'S)-5-((1S)-1-methyl-2-hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide

Using the procedure of Example 41, except substituting
20 2(S)-t-butyldimethylsiloxy-1-methylethanol in 41(a) (prepared from 2(S)-1,2-propanediol), the title compound was prepared.

NMR(CD3OD) & 7.38-6.90 (10H, m), 6.83 (2H, s), 4.58 (2H, m),

3.61 (1H, m), 3.34 (3H, m), 2.82-2.44 (5H, m), 2.00 (1H, m),

1.66 (1H, m), 1.52 (1H, m), 1.08 (3H, d), 0.85 (3H, d), 0.60

25 (3H, d).

Example 57

Preparation of (2R.4S.5S.1'S)-5-((1R)-1-methyl-2- (hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide

Using the procedure of Example 41, except substituting 2(R)-t-butyldimethylsiloxy-1-methylethanol in 41(a), the title compound was prepared. NMR(CD3OD) δ 7.39-6.88 (10H, m), 6.82 (2H, s), 4.56 (2H, m), 3.60 (1H, m), 3.36 (3H, m), 2.81-2.45 (5H, m), 1.99 (1H, m), 1.65 (1H, m), 1.51 (1H, m),

1.03 (3H, d), 0.84 (3H, d), 0.60, (3H, d)....

. (1.17) to seed to an Example 58

Preparation of (2R.4S.5S.1'S)-5-((1-acetyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

. The grant 1884 formed to now be proposed of the grant of

5 phenylmethylhexanamide

The title compound was prepared by the procedure of Example 13(a)-(c), except substituting acetic anhydride in place of isopropyl chloroformate. NMR(CD3OD) δ 7.21-6.90 (10H, m), 6.81 (2H, s), 4.58 (1H, d), 3.98 (1H, m), 3.51 (1H, m), 2.85-2.49 (5H, m), 1.99 (1H, m), 1.68 (3H, s), 1.61 (3H,

. (t) m), 1.50 (1H, m), 0.80 (3H, d), 0.60 (3H, d).

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Strategie (1996 Strategie (1886) A. Francisco (1886) A. Francisco (1886)

- Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-(4-benzyloxyphenylmethyl) hexanamide
 - a) (3R,5S,1'S)-(1'-t-butoxycarbonylamino-2'-phenyl)ethyl-3-20...(4-benzyloxy)phenylmethyl-tetrahydrofuran-2-one 200 62
- (4-benzyloxy)benzyl bromide, the title compound was prepared (284 mg, 27%). NMR(CDCl3) & 7.48-6.72 (14H, m), 4.94 (2H,
 - on es s), 4.43% (1H, d) 7% 4% 12 (1H, dd), 3.83 (1H, q), 2.97-2.62 (5H, %), 2.12% (1H, m), 1.85% (1H, m), 1.27 (9H, %).
 - (p.,100b) (2R,4S,5S)=5-(t-butoxycarbonyl) amino-4-t-butyldimethyl-, 100 siloxy-6-phenyl-2-(4-benzyloxyphenylmethyl) hexanoic acid Folowing the procedure of Evans et al., J. Org. Chem.

APP OF STATE OF STATE OF THE (STA STATE OF STATE

30 50, 4615 (1985), except substituting the compound of Example 59(a) for benzyl bromide, the title compound was prepared.

NMR(CDCl3) δ 7.42-6.76 (14H, m), 4.99 (2H, s), 4.69 (1H, d),

3.91 (1H, q), 3.66 (1H, m), 2.98-2.36 (5H, m), 1.85 (1H, m),

1.52 (1H, m), 1.30 (9H, s), 0.88 (9H, s), 0.04 (6H, m).

recorded to the control of the control of the Market and the control of the contr

c) (2R, 4S; 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl6-phenyl-2-(4-benzyloxyphenylmethyl) hexanamide

Following the procedure of Example 12(c), except using (b), the title compound was prepared (284 mg, 92%).

NMR(CDCl3) δ 7.42-6.74 (16H, m), 5.042(2H, s), 4.99 (1H, d),

4.77 (1H, d), 4.51 (1H, dd), 3.93 (1H, q), 2.3069 (1H, m),

5 2.80-2.39 (5H, m), 1.81 (1H, m), 1.62 (1H, m), 1.33 (9H, s),

0.92 (9H, s), 0.75 (6H, dd), 0.07 (6H, d) 1.00

d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-(4-0);

10 benzyloxyphenylmethyl) hexanamide (...) 24.5-28.3 (at 0.)

Following the procedure of 12(d), except using (c), the title compound was prepared (100 mg, 94%). NMR(CD3OD) δ 7.41-7.09 (10H, m), 6.85 (2H, d), 6.79 (2H, s), 6.58 (2H, d), 5.41 (1H, d), 4.90 (2H, s), 4.47 (1H, d), 3.62 (1H, q), 3.48 (1H, d), 2.79-2.48 (6H, m), 2.02 (1H, m), 1.62 (2H, m), 1.33 (9H, s), 0.74 (3H, d), 0.61 (3H, d).

Example 60

which is a life of the constraint and the constraint

・ のかついすいものが知り、 (b)

- 25 the compound of 59(d), the title compound was prepared (56 mg, 86%). NMR(CD3OD) δ 7.18 (5H, m), 6.84 (2H, s), 6.73 (2H, d), 6.44 (2H, d), 5.32 (1H, d), 4.45 (1H73d), 3.61 ((1H, q), 3.42 (1H, m), 2.80-2.42 (5H, m), 2.04 (1H, m), 1.61 (2H, m), 1.31 (9H, s), 0.70 (3H, d), 0.61 (3H, d) 2.80 (2H, d)

2013 to 1 Symme (1381) dill 600 (600) dill 600 (600

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10.00 (a. Od. 10.0 (A. E. Gr. 50.00)

Preparation of (2R:4S.5S)-5-(t-butoxycarbonyl)amino-4hydroxy-2-phenylmethyl-6-phenyl-N-[1:-cyclopropyl-1:-

35 imidazol-2-vllmethvl-hexanamide

a) α -(t-butoxycarbonyl)-amino- α -cyclopropylacetonitrile

(基度はおからため、はたが、たられるなどのできる。

To a solution of cyclopropylmethanol (10.2 g, 141 mmol)

ive of in methylene chloride (250 mL) sodium acetate (1 g) and 20 g

of Celite® were added. Pyridinium chlorochromate (30 g, 140

mmol) was added in small portions over a period of 30 m.

5. After 1 h the reaction mixture was diluted with ether (100mL), filtered through Celite® and washed with ether. The combined organic extracts (1 L) were concentrated in vacuo at 15-18°C to yield formyl cyclopropane.

The crude aldehyde was dissolved in water (50 mL), and ammonium chloride (6.51 g), potassium cyanide (7.16 g) and aqueous ammonium hydroxide (100 mL, 28% w/w). The reaction mixture was stirred at room temperature overnight, extracted with ethyl acetate, and the combined organic extracts were dried over MgSO4. Filtration and evaporation of the solvent in vacuo yielded α-amino-α-cyclopropyl acetonitrile as an

oil. with rein conday elife es income a come a self (5

To a solution of the crude aminonitrile (2 g) in THF (20 mL) di-tert-butyldicarbonate (1.53 g, 7 mmol) was added. The reaction was stirred overnight. Removal of the solvent in 20 vacuo followed by flash chromatography (silica, 1:8 ethyl acetate:hexane) yielded the title compound (2.8 g). ¹H NMR (CDCl₃, 200 MHz) δ 5.0 (bs, 1H), 4.4 (bs, 1H), 1.4 (s, 9H), 1.2 (m, 1H), 0.7 (m, 2H), 0.5 (m, 2H).

To a solution of the compound of Example 61(a) (1 g, 5.1 mmol) in THF (20 mL), diisobutylaluminium hydride (10.5 mL, 10.5 mmol, 1M in THF) was added at -78°C, over 5 min. The reaction mixture was allowed to warm to 0°C over a period of 2 h, and stirred at 0°C for an additional 1 h. The reaction mixture was quenched with MeOH (2 mL), and saturated potassium sodium tartrate solution (100 mL) was added.

**Extraction with ether, drying over MgSO4 and removal of solvents in vacuo yielded an oil.: Flash chromatography 35 (silica, 1:10 ethyl acetate:hexane) gave the title compound as a colorless solid (225 mg). NMR(CDCl3, 400 MHz) & 9.45 (bs, 1H), 4.95 (bs, 1H), 3.5 (bs, 1H), 1.3 (s, 9H), 0.7 (m, 1H), 0.3-0.6 (m, 4H).

1:

c) 1-(t-butoxycarbonyl)amino-1-(imidazol-2-yl)-1-cyclopropyl-The state of the state of the methane

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A mixture of the compound of Example 61(b) (178 mg, 0.89 mmol), glyoxal (150 mL, 1 mmol, 40% aq), ammonium hydroxide (5 mL, 28% aq) and MeOH (5mL) was stirred at room temperature for 10 h. The solvents were removed in vacuo and the residue was titurated with ether to yield a brown solid (53 mg). solid was passed through Florisil® and eluted with 5% 10 MeOH/methylene chloride. Removal of the solvent in vacuo followed by trituration provided the title compound as a colorless solid (19 mg). MS(CI/NH3) m/e 238.3 [M+H]+. 1H NMR (CD₃OD, 200 MHz) δ 6.9 (s, 2H), 4.1; (bd, 1H), 1.4 (s, 9H), 1.3 (m, 1H), 0.6 (m, 2H), 0.4 (m, 2H) Negle (1996)

: 15 d) 1-amino-1-(imidazol-2-yl)-1-cyclopropyl-methene, ... The second of the second of the second

trifluoroacetate.

The compound of Example 61(c) (15 mg) was dissolved in 1 mL of TFA and stirred at room temperature for 20 min.

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- 20 Solvents removed in vacuo to give the title compound as a semisolid residue. ¹H NMR(CD₃OD, 200 MHz) δ 7.1 (s, 2H), 3.8 (d, 1H, J=7 Hz), 1.5 (m, 1H), 0.5-0.8 (m, 4H).
- e) (2R, 4S, 5S)-5-(t-butoxycarbonyl)amino-4-(t-butyldimethyl)-25 siloxy-2-phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-

The compound of Example 61(d) was dissolved in DMF (2 mL) and NMM (26 mg, 0.25 mmol) was added and the solution was stirred at 0°C for 30 min. (2R,4S,5S)-2-phenylmethyl-4-(tbutyldimethyl) siloxy-5-(t-butoxycarbonyl) amino-6-phenyl hexanoic acid (38 mg, 0.07 mmol) and BOP@reagent@(30 mg, 0.07 mmol) were added and the reaction was stirred at room temperature for 24 h. The reaction was diluted with ethyl acetate (100 mL), washed with aqueous sodium bicarbonate and ::35 dried over anhydrous potassium carbonates: Removal of solvents in vacuo, followed by flash chromatography (silica, 5% methanol/methylene chloride) yielded the title compound as

a mixture of diastereomers (25 mg) 46 cm (0-2.0 cm)

: .

phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2-yl]methyl-hexanamide

1.

The compound of Example 61(c) was dissolved in THF (2 mL) and tetrabutyl ammonium fluoride (200mL, 1M in THF) was added. The reaction was stirred at room temperature overnight and methylene; chloride (100 mL) and water (10 mL) were added. The organic layer was dried over potassium

carbonate, and the solvent was removed in vacuo to give an oil. Flash chromatography (silica, 5% methanol/methylene chloride) gave a colorless solid which was a 1:1 diastereomeric mixture of the title compound.

Example 62

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Preparation of (2R.4S.5S.1'R)-5-(t-butoxycarbonyl) amino-4hydroxy-2-phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-

- 20 (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-2phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2yllmethyl-hexanamide
- 25 61(e) by flash chromatography (silica, 3% methylene chloride/methanol), yielded 48 mg of isomer 1, 15 mg of familiationer 2 and 20 mg of combined fractions. 1H NMR for isomer 1, 15 mg of familiationer 2 and 20 mg of combined fractions. 1H NMR for isomer 1, 16 mg 1, 400 MHz) 87.1-7.4 (m, 10H), 6.95 (s, 2H), 6.1 (d, 2H), 4.85 (d, 1H), 4.15 (dd, 1H), 3.75(q, 1H), 3.6(m, 1H), 30 mg 2.9 (dd, 1H), 12.7 (d, 2H), 2.6 (dd, 1H), 2.3 (m, 1H), 2.0 (m, 2H), 1.6 (m, 1H), 1.4 (m, 1H), 1.35 (s, 9H), 0.95 (s, 9H), 0.7 (m, 2H), 10.4 (m, 1H), 0.25 (m, 1H), 0.1 (m, 1H), 0.2 (s, 3H), 0.1 (s, 3H), 1H, NMR for isomer 2 (CDCl₃, 400 MHz) 87.1-27 (m, 10H), 6.8 (s, 2H), 6.26 (d, 1H), 4.6 (d, 1H), 4.0 (m, 35 2H), 2.5-3.0 (m, 4H), 1.8 (m, 1H), 1.7 (m, 1H), 1.5 (m, 1H), 1.4 (s, 9H), 1.0 (s, 9H), 0.7 (m, 2H), 0.2 (m, 2H), 0.1 (2 overlapping singlets, 6H).

25

30

b) Following the procedure of Example 61(f), except substituting the compounds of Example 62 (a) yielded the title compounds. 1H NMR for isomer 1 (CD3OD, 400 MHz) \$57.1-7.3 (m, 10H), 6.95 (s, 2H), 4.25 (d, 1H), 3.5-3.7 (m, 2H), 2.5-3.0 (m, 5H), 1.7 (m, 2H), 1.4 (s, 9H), 1:1 (m, 1H), 0.6 (m, 1H), 0.25-0.4 (m, 2H), 0.05 (m, 1H); MS (ESMS) m/e 533.2 [M+H]+; 1H NMR for isomer 2 (CD3OD) & 7.1-7.4 (m; 10H), 6.85 (s, 2H), 4.25 (d, 1H), 3.5-3.7 (m, 2H); 2.5-2.9 (m, 5H), 1.5-1.8 (m, 2H), 1.4 (s, 9H), 1.1 (m, 1H), 0:2-0.6 (m, 4H); MS(ESMS) m/e Were the transfer of the option 10 533.4 [M+H]+. v marryes are productive tropics. The sec

Example 63. SMAD FOR SIGNATION

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Preparation of (2R, 4S, 5S, 1'S) -5-((isopropylthiol) carbonyl)amino-4-hydroxy-2-phenylmethyl-6-phenyl-N-[1-isopropyl-1'imidazol-2-vllmethyl-hexanamide v (egg (88, 9)) (9 th Parabilitat samit

a) 5-((isopropylthiol)carbonyl)amino-4-(t-19 complete butyldimethylsiloxy) -2-phenylmethyl-6-phenyl-N-[1'-isopropyl-1'-(1-(isopropylthiol)carbonyl-imidazol-2yl)]methylthe specific terms the metal state of the first terms to hexanamide

To a solution of (2R, 4S, 5S, 1'S) -5-amino-4-t- 4Y butyldimethylsiloxy-2-phenylmethyl-6-phenyl-N-[1'-isopropyl-1'-imidazol-2-yl]methyl-hexanamide (81 mg, 148 mmol) and DMAP (37 mg, 303 mmol) in dichloromethane (8:mL), 30 (5:10 isopropylthiolchloroformate (42 mg, .303 mmol) in dichloromethane (1.mL) was added. The solution was stirred for 20 h and an additional equivalent of the chloroformate and DMAP were added. The reaction mixture was stirred for an additional 20 h, diluted with dichloromethane, and washed with saturated sodium bicarbonate. The organic extract was dried over magnesium sulfate, filtered and evaporated to an oil. The oil was dissolved in chloroform and purified by flash chromatography (silica, 1% methanol/chloroform) to give 35 the title compound as an oil (79.5 mg)

hydroxy-2-phenylmethyl-6-phenyl-N-[1-isopropyl-1'-imidazol-2-yl]methyl-hexanamide

yl]methyl-hexanamide

To a solution of the compound of Example 63(a) (79 mg,
105 mmol) in methanol (8 mL), 10% hydrochloric acid (3 mL)

was added. The reaction mixture was stirred overnight at
25°C. The methanol was evaporated in vacuo, and the residue

was diluted with water. The solution was neutralized with 5%

aqueous sodium carbonate, and a solid precipitated. The
solid was filtered, washed with water, and triturated with

compound (27 mg, 48%). NMR(CDCl3, 250 MHz) & 6.9-7.3 (m,
10H), 6.85 (s, 2H), 6.20 (d, 1H), 4.42 (d, 1H), 4.22 (m, 1H),
4.0 (m, 1H), 3.55 (m, 3H), 2.5-3.0 (m, 6H), 1.65 (t, 2H),

1.27 (m, 7H), 71 (d of d, 6H); MS(FAB) m/e 537 [M+H]+; TLC

Rf 0.30 (silica, 4% methanol/chloroform).

Example 64

Preparation of (2R.4S.5S.1'S)5-(1-hydroxymethyl-(Ar all Acyclopentyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexamide

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b) 1-(t-butyldimethylsiloxy) methyl-cyclopentyl 4-nitrophenyl carbonate

A solution of the compound of 64(a) (1.15 g, 5 mmol),

DMAP (0.611 g, 5 mmol) and bis (4-nitrophenyl) carbonate (1.52

g, 5 mmol) in dichloromethane (16 mL) was stirred overnight

at 25°C. The reaction mixture was diluted with

dichloromethane and washed with 5% sodium carbonate. The

solvent was removed at reduced pressure and the residual oil

was triturated with hexane:ethyl acetate (3:2) and filtered.

The product was purified by flash chromatography (silica,

19:1 hexane:ethyl acetate) to give a colorless oil (0.599 g,

30%).

5.85 (n . n .

c) (2R,4S,5S,1'5)-5-[1-(t-butyldimethylsiloxy) methyl
15 cyclopentyloxycarbonyl]amino-4-t-butyldimethylsiloxy-N-[1'
isopropyl-1'-(t-butyldimethylsiloxy) methyl
cyclopentyloxy) imidazol-2-yl]-6-phenyl-2-phenylmethyl
hexanamide

A solution of the compound of Example 13(a) (173 mg, 0.316 mmol), DMAP (81 mg, 0.663 mmol) and the compound of Example 64(b) (262 mg, 0.663 mmol) in dichloromethane (10 mL) was stirred for 48 h at 25°C. The organic solution was diluted with dichloromethane, washed with 5% sodium carbonate solution and the solvent removed at reduced pressure. The product was purified by flash chromatography (silica, 4:1hexane:ethyl acetate) to yield the title compound as an oil (200 mg, 60%).

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d) (2R,4S,5S,1'S)5-(1-hydroxymethyl-cyclopentyloxy-carbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexamide

A solution of the silated derivative (200 mg, 0.188 mmol) in methanol (7 mL) and 3N HCl (2.5 mL) was stirred overnight at 25°C. The methanol was removed at reduced pressure and the solution was diluted with water (15 mL) and extracted with ether (25 mL). The aqueous solution was neutralized with 5% sodium carbonate solution to pH 7-7.5 and the product precipitated as a solid. The solid was filtered,

washed with water and dried in vacuo to yield the title compound (51 mg, 47%). NMR (CD3OD, 400 MHz) δ 7.0-7.3 (m, 10H), 6.87 (s, 2H), 4.62 (d, 1H), 3.70 (m, 3H), 3.55 (d, 1H), 2.5-2.9 (m, 5H), 2.05 (m, 1H), 1.5-2.0 (br, 10H); 0.88 (d, 3H), 0.70 (d, 3H); TLC R_f 0.50 (silica, 8% methanol/chloroform).

to the control of the state of the state of Example 65

- Preparation of (2R,4S,5S,1'S)-5-[3-(R)-(1H-imidazol-2-yl)-3hydroxy-4-methylpentylamidol-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide; and
 (2R,4S,5S,1'S)-5-[3-(S)-(1H-imidazol-2-yl)-3-hydroxy-4methylpentylamidol-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
- 15. vl)methyl-6-phenyl-2-phenylmethyl-hexanamide
- HE CONTRACTOR SECTION SECTION OF A SECTION OF A (a) 1-(1-benzyloxymethylimidazol-2-yl)-2-methyl-1-propanol 1 100 700 - 1-benzyloxymethylimidazole prepared according to the procedure of Ngochindo, R., J. Chem. Res. (S), 58 (1990)) \approx 02 20 0 (3.76 g, 20 mmol), and THF (40 mL) at -40°C, was treated , dropwise with n-BuLi (8.4 mL, 21 mmol, 2.5M in hexane). The get resulting solution was stirred at:-40°C for 15 min, and i-Managerbutyraldehyde (2.0 mL, 22 mmol) was added dropwise. The at a reaction was stirred at -40°C for 1.5 h, 0°C for 1 h, warmed 25 to 23°C, poured into H2O, and extracted with EtOAc. The combined extracts were washed with brine, dried (Na2SO4) and with regist concentrated in vacuo. Trituration of the residue with Et20/hexane gave a white solid which was dried in vacuo overnight to afford of the title compound (3.57 g, 69%). 30 NMR (CDCl₃, 400 MHz) δ 7.28 (m, 5H), 6.97 (s, 1H), 6.92 (s, IN. 1H), 5.23 (d, 1H, J=12 Hz), 5.42 (d, 1H, J=12 Hz), 4.48 (s, 2H), 4.44 (d, 1H, J=9 Hz), 2.21a (m, 1H), 1.02 (d, 3H, J=77 2 Hz) , 1 0 .83 (d, : 3H, J=7 Hz) . (c, : 20) . (c) . (c)

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added and stirring was continued for an additional 2 d. Filtration through Celite®, concentration and flash chromatography (silica, 0-1% CH3OH/CH2Cl2) afforded the title compound (0.773 g, 77%). 1H NMR (CDC13, 400 MHz)-7.28 (m, 6H), 7.18 (s, 1H), 5.85 (s, 2H), 4.52 (s, 2H), 3.94 (m, 1H), mechanicaldy longitum. 1.21 (d, 2H, J=5 Hz).

c) t-butyl 3-(1-benzyloxymethylimidazol-2-yl)-3-hydroxy-4methyl-pentanoate

Diisopropylamine (83 µL, 0.59 mmol) and THF1 (1.5 mL) were cooled to -40°C and n-BuLik (188 µL to 0.47 mmol, 2.5M in hexane) was added. The reaction mixture was warmed to -10°C and stirred for 15 m/ recooled to -70°C and t-butyl acetate (63 μL, 0.47 mmol) was added. The reaction was stirred for 5 m, and HMPA (254 μL, 1.41 mmol) was added The reaction was stirred at -70°C for 5 m and 1-(benzyloxymethylimidazol-2yl)-2-methyl-propan-1-one (100 mg/m0:39 mmol) in THF (1.5 mL) was added dropwise. The mixture was stirred at -70°C for 30 m, -40°C for 30 m, -10°C for 30 m, swarmed to 23°C, poured 20 into 10% aqueous K2CO3 and extracted with EtOAc. The combined organic extracts were washed with brine, dried (K2CO3), concentrated and flash chromatographed (silica gel, step gradient, 0-20% EtOAc/hexanes) to afford the title compound in the control (131 mg, 90%). 1H NMR(CDCl3, 2400 MHz) δ 7:25 (m, 55H), 6.96 25 (s, 1H), 6.91 (s, 1H), 5.69 (d, 1H, J-10 Hz), 5.65 (d, 1H, J=10 Hz), 4.53 (d, 1H, J=11 Hz), 4.48 (d, 1H, J=11 Hz), 3.23 (d, 1H, J=6 Hz), 2.57 (d, 1H, J=6 Hz), 2.14 (m, 1H), 1.39 (s, 9H); 0'.97 (d, 3H, J=7 Hz); 0.75 (d, 3H, 5 J=7 Hz); MS(ES) m/e the first on bank of it adjancers. 375 [M+H]+.

> d) 3-(1-benzyloxymethylimidazol-2-yl)-3-hydroxy-4-methyl pentanoic acid triflouroacetate to All . O . P. 1015

The compound of Example: 65(c) (93 mg. 0.24 mmol) was dissolved in TFA (1 mL) and stirred for 20 m. The TFA was removed in vacuo to give the title compound (102 mg;d 100%). 1H NMR (CDC13, 400 MHz) 7.30 (m, 7H); 6.06 (d, 1) H, J=9 Hz), 5.74 (d, 1H, J=1 Hz), 4.67 (d; 1H, J=9 Hz), 4.612 (d, 1H, J=9 Hz), 3.62 (d, 1H, J=12 Hz), 2.93 (d, 1H, J=12 Hz), 2.04 (m,

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To test 1H), 0.92 (d, 3H, J=12 Hz), 0.88 (d, 3H, J=12 Hz); MS(ES) m/e 6.5361 (eq. 319 [M+H] + 50; eq. 4362 (eq. 319 [M+H] + 50
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- N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2
 - phenylmethyl-hexanamide : :: :::
- -: Y :0 : A mikture of the compound of Example 65(d) (1.0 eq)

 (2R,4S,5S,1'S)-5-amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-
- 13.310 .2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide (1.1 eq), BOP .(... reagent (1.1 eq), and triethylamine (4 eq) were reacted
- (III) according to the procedure of Example 1(c). The product was
 - (57%) (silica, step gradient, 0-4% CH₃OH/CH₂Cl₂). ¹H
 - 15 NMR (CDC1₃, 400 MHz) δ 7.36-6.76 (m, 19H), 5.65 (m, 2H), 4.66
 - (m, 1/2H), 4.51, (m, 2H), 4.39 (m, 1/2H), 4.30 (m, 1/2H), 4.02 (m, 1/2H), 3.68 (m, 1H), 3.28 (m, 1H), 2.90-2.35 (m, 6H),
- 2.13 (m, 1H), 1.76 (m, 1/2H), 1.68 (m, 1/2H), 1.40 (m, 1/2H),
- 1.00-0.70 (m, 21H), 0.10-0.00 (m, 6H); MS(ES) m/e 849 [M+H]+.
- (Bi20,a) with a field any flow for dividing the property of the property.
- (WS.1 ...) f) ...(2R, 4S, 5S, 1.!S) =5-[3-(RS)-(1-benzyloxymethylimidazol-2-yl)-3-hydroxy-4-methylpentanoyl]amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

 The compound of Example 65(e) (100 mg, 0.12 mmol) was
- 25 desilylated by the procedure of 47(c) to cleanly afford the title compound (78 mg, 89%). 1H NMR(CDCl3, 400 MHz) 8 7.40
 - m6.80 (m, 19H), 5.75 (m, 2H), 4.97 (m, 1/2H), 4.78 (m, 1/2H),
 - 4.51 (m, 2H) 3.94 (m, 1/2H), 3.85 (m, 1/2H), 3.51 (m, 1H),
 - 3.21 (m, 1H), 2.97-2.43 (m, 6H); 2.00 (m, 1H), 1.60 (m, 1H),
 - -30: -1.43 (m, 1H) : 0.97-0.49 (m, 12H); MS(ES) m/e: 735 [M+H]+:
- -fyddesig) (2R,4S,5S;1'S)-5-[3(R),-(imidazol-2-yl)-3-hydroxy-4-methylpentanoyl]amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-
- galas: 2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide; and

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- -:-135 ala (2R, 4S, 5S, 1'S) -5-[3-(S) (imidazol-2-yl) -3-hydroxy-4-
- Ly its methylpentanoyl]amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-541 (2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

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Using the procedure of Example 47(d), the compound of Example 65(f) (72 mg, 0.98 mmol) was hydrogenated to afford a diastereomeric mixture of the title compounds. The mixture was purified by flash chromatography (silica, step gradient, 0-8% CH3OH/CH2Cl21 to afford tail fractions; containing the pure diastereomers (35 mg total, 58%) . (1977) 11 41

Isomer 1, last eluting, (2R, 4S, 5S, 1'S) -5-[3-(R)-(1H-Imidazol-2-yl)-3-hydroxy-4-methylpentylamido]-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide. ¹H NMR(CDCl₃, 400! MHz) & 7.35-6.82 (m, 10H), 6.93 (s, 1H), 6.84 (s, 1H), 4.42 (d, 1H, J=9 Hz), 3.77 (m, 1H), 3.40 (m, 1H), 3.00-2.40 (m, 5H), 2.14 (m, 1H), 1.99 (m, 1H), 1.56 (m, 1H), 1.47 (m, 1H), 0.93-0.64 (m, 12H); MS(ES) m/e 615 [M+H]+.

> Isomer 2, first eluting, (2R, 4S, 5S, 1'S)-5-[3(S)-(1H-Imidazol-2-yl)-3-hydroxy-4-methylpentylamido]-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide. ¹H NMR(CDCl₃, 400 MHz) δ 7.35-6.81 (m, 10H), 6.83 (s, 1H), 6.81 (s, 1H), 4.46 (d, 1 H, J=9 Hz),3.93 (m, 1H), 3.40 (m, 1H), 3.00-2.40 (m, 5H), 2.13 (m, 1H), 1.91 (m, 1H), 1.41 (m, 1H), 1.10 (m, 1H), 0.93-0.64 (m, 12H); MS(ES) m/e 615 [M+H]+.

Example 66 r. Alteria

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Preparation of (2R.4S.5S.1'S)-5-[(4-methoxyphenoxy)carbonvllamino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-phenylmethyl-hexanamide and the art of the latest

great the second of the second of the second

30 a) (2R, 4S, 5S, 1'S) -5-[(4-methoxyphenoxy) carbony1]amino-4-tbutyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-' methoxycarbonyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethylgive in this type have by ask hexanamide

Following the procedure of Example (13 (b) ; except using p-methoxyphenyl chloroformate and (2R, 4S, 5S, 1'S)-5-amino-4-tbutyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide (114 mg, 0.21 mmol), the title compound was prepared (63%). NMR (CDCl3), & 7.44-6.76

(s,3H), 3.76 (m, (1H), 3.73 (s, 3H), 2.96-2.50 (m, 5H), 2.05 (m, 5H), 1.60 (m, 1H), 0.94 (s, 9H), 0.79 (d, 3 H, J=7 Hz), **** (****0.74. (s, ;3H); 0.12. (s, '3H) = 0.11e (s, :3H) :. - :

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(1'- tb) (2R, 4S, 5S, 1'S) -5- (methoxycarbonyl) amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylthe street hexanamide to be the second to be the there is a reason different

Following the procedure of Example 13(c), except using so 10 or the compound of Example 66(a), the title compound was at prepared (32%). NMR(CDCl3/CD3OD), δ 7.36-6.84 (m, 16H), 4.49 (d, 1H, J=9 Hz), 3.79 (s, 3H), 3.37 (m, 1H), 2.92-2.60 (m, 5H), 2.10-1.70 (m, 3H), 0.78 (d, 3H, J=7 Hz), 0.67 (d, 3H, (a J=7 Hz); MS(ES) m/e 585 [M+H]+.

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Preparation of (2R.4S.5S.1'S)-5-(t-butylaminocarbonyl)amino -4-hvdroxy-N-(1'-isopropyl-1'-imidazol-2-v1)methvl-6-

20 phenylmethyl-hexanamide

a) (2R, 4S, 5S, 1'S) 5-(t-butylaminocarbonyl) amino-4-(tbutyldimethylsiloxy)-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide 1997 to lyoner grant and a

: (2025 7'f) The compound of Example 13(a) (0.13 g, 0.24 mmol) was dissolved in dichloromethane (3 mL) and t-butyl isocyanate 13 (0.028 g, 0.29 mmol) was added. After stirring at 30°C for * * * Nhard 18 th, the solvent was removed under reduced pressure and the (cl.: residue was chromatographed (silica, 2:3 ethylacetate:hexane) .30 . to give the title compound as a white solid (0.12 g, 77%). ** ** NMR (CDC13) (δ.7.35-7.05) (12H, m), 6.85 (2H, s), 4.69 (1H, d,

J=9 Hz), 4.60 (1H, t, J=8 Hz), 4.38 (1H, br), 4.24 (1H, q, J=8 Hz), 3.66 (1H, dd, J=4 Hz, 10 Hz), 2.95 (1H, dd, J=9Hz, 13Hz), 2.73(2H, m), 2.54 (1H, dd, J=5 Hz, 13 Hz), 2.42 (1H,

m), 1.82 (1H, m), 1.67 (1H, m), 1.22 (9H, s), 0.93 (9H, s),

0.071 (3H, 4s); MS(ES) m/e 648.4 [M+H] +. 1. 1. 1. 1. 1. 1. 1. 1. 1.

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(2R, 4S, 5S, 1'S)-5-(t-butylaminocarbonyl)amino-4-hydroxy-N-(d, 1, 7) 2: (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-(a) (a) 1.60 (a) 18; (.e. 12; (.e. 1 (x!) : hexanamide.

The compound of Example 67(a): (0.033£g, ~0.05 mmol) was stirred in dry THF (0.25 mL) and tetrabutylammonium flouride (0.25 mL, 0.25 mmol) invTHF was added: After 18 h.at 50°C the reaction was cooled, diluted with ethyl acetate (25 mL), washed with water (5 mL), and dried (MgSO4) in The combined organic extracts were filtered and concentrated in vacuo. 10 Chromatography (silica, 1:1 ethyl:acetate:hexane) gave the title compound as a white solid (0.018 g, 66%) . M.p 226°C (dec); NMR(CD3OD), δ 7.37-6.90 (10H, m) (6.90 (2H, (s)), 4.58 (1) (1H, d, J=9 Hz), 3.71 (1H, t, J=7 Hz), 3.52 (1H, d, J=9 Hz), 2.75 (4H, m), 2.53 (1H, dd, J=4; Hz/; 12; Hz); 2.03 ((1H, m), 1.76 (1H, m), 1.66 (1H, m), 1.22 (9H, s), 0.79 (3H, d, J=7 Hz), 0.67 (3H, d, J=7 Hz); MS(ES) m/e 534 [M+H] $^+$.

Example 68 1 For the tax of the second the s the control of the second sections of the section section section section section section section section secti

Preparation of (2R.4S.5S.1'S)-5-(methylaminocarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-v1)methyl-6phenylmethyl-hexanamide.

Following the procedure of Examples 67(a)-67(b), except substituting methyl isocyanate for t-butylisocyanate, the r 25 title compound was prepared (0.075 mg, 51%) .sitMp 253°C (dec); NMR (DMSOd6) 87.78 (1H, d, J=9 Hz), 7.80-6.96 (11H, m), 6.88 (2H, S), 5.78 (1H, d, J=5 Hz), 5/72 (1H, d, J=9 Hz), 4.84 (1H, d, J=4 Hz), 4.65 (1H, m), 3.68 (1H, cq, J=7 Hz), 3.44 (1H, br), 2.74 (3H, m), 2.58 (1H, dd, J=7 Hz, 13 Hz), 2.50 30 (3H, s), 2.41 (1H, d, J=8 Hz), 1.92 5(1H, m), 1.46 (2H, m), 0.72 (3H, d, J=7 Hz), 0.63 (3H, d, J=7 Hz), MS (ES) m/e 492 $[M+H]^+$. Sept. 25. 4. 40 (13), 2, ... 10:1, 4

> 2. 1 . 15 (1.15 (1.15) do 1. 1 (1.15) Example 69, asyst 3 , and a 2017, 1912 (2, (85) 98.4 (m

> > Secretary and the second of

Preparation of (2R.4S.5S.1'S)-5-(phenylaminocarbonyl)amino-4hvdroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-: () phenylmethyl-hexamide.

Following the procedure of Examples 67(a)-67(b), except substituting phenyl isocyanate for t-butylisocyonate, the title compound was prepared (87 mg, 79%). Mp 273°C (dec); NMR(DMSO-d6), 8.50 (1H; s), 7.81 (1H, d, J=9 Hz), 7.34-6.83

5 (18H, m), 6.07 (1H, d, J=9 Hz), 4.99 (1H, d, J=4 Hz), 4.65 (1H, t, J=8 Hz), 3.75 (1H, m), 3.52 (1H, br), 2.77 (3H, m), 2.66 (1H, m), 2.42 (1H, d, J=7 Hz), 1.89 (1H, m), 1.50 (2H, m), 0.68 (3H, d, J=7 Hz), 0.61 (3H, d, J=7 Hz); MS (DCI/NH3) m/e 554.3 [M+H]+.

(2R,4S,5S,1'S)-5-N-(propylaminocarbonyl)amino-4-hydroxy-N(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-

15 hexamide.

Following the procedure of Examples 67(a), except substituting n-propyl isocyanate for t-butylisocyanate, the title compound was prepared (0.048 g, 54%). Mp 247-9°C (dec); NMR(DMSO-d6) &7.75 (1H, d, J=8 Hz), 7.23-6.94 (11H, 20 m), 6.85 (2H, s), 5.87 (1H, t, J=5 Hz), 5.65 (1H, d, J=9 Hz), 4.82 (1H, d, J=4 Hz), 4.64 (1H, t, J=8 Hz), 3.66 (1H, m), 3.38 (1H, br), 2.87 (2H, q, J=6 Hz), 2.74 (3H, m), 2.56 (1H, dd, J=7 Hz, 13 Hz), 2.39 (1H, d, J=7 Hz), 1.91 (1H, m), 1.43 (2H, m), 1.28 (2H, q, J=7 Hz), 0.77 (3H, t, J=7 Hz), 0.71 (3H, d, J=7 Hz), 0.62 (3H, d, J=7 Hz); MS(CI) m/e 520.2

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The to [M+H] . The transfer was as a to

(b) 0°27Following the method of Example 67(a)-67(b), except (b) 35 (prepared (0.012 g, 21%)) Mp. 195-7°C (dec); NMR (CD3OD) & 4.57.32-6.86 (12H, m), 4.59 (1H, m), 3.64 (1H, br), 3.34 (2H, br), 2.79 (5H, m), 2.03 (1H, m), 1.73 (1H, m), 1.58 (3H, m),

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0.92 (3H, t, J=7Hz), 0.83 (3H, d, J=7Hz), 0, 68 (3H, d, J=7 m/e 536.2 [M+H]+.1 v and pello a decare Hz); MS (CI) in the management of the

Example 72.8 (35-00.00) 2.00

or any co. or the above &

Preparation of (2R.4S.5S.1'S)-5-(isopropylaminocarbonyl)amino-4-hydroxy-N- (1'-isopropyl-1'-imidazol-2-yl)methyl-6-

Following the method of Example 67(a)-67(b), except substituting isopropyl isocyanate for t-butyl isocyanate, the title compound was prepared (0.034g, 46%). NMR(DMSO-d6) δ 7.78 (1H, d, J=8 Hz), 7.24-6.97 (11H, m), 6.85 (2H, s), 5.74 (1H, d, J=8 Hz), 5.57 (1H, d, J=9-Hz), 4.83 (1H, d, J=4 Hz), 4.66 (1H, d, J=7 Hz), 3.62 (2H, m), 3.43 (1H, br), 2.73 (3H, 15 m), 2.57 (1H, dd, J=7 Hz, 13.5 Hz), 2.41 (1H, d, J=7 Hz), 1.91 (1H, m), 1.45 (2H, m), 0.95 (3H, d; J=6.5 Hz), 0.93 (3H, d, J=6.5 Hz), 0.72 (3H, d, J=6.5 Hz); 0.63 (3H; d, J=6.5 Hz); MS (CI) m/er 520.2 [M+H]+. W of ag ag the base as a cultiout of the control of the control

Example 73 vs (BS) (E.B v. :

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Preparation of (2R.4S.5S.1'S)-5-(aminocarbonyl) amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-(Ja. 30, 1.20 (J. 3) at the phenvlmethvl-hexamide

The compound of Example 67(a) (0.050 g; 0.094 mmol) was dissolved in triflouroacetic acid (2 mL) and stirred at 50°C for 2 h. After cooling, the reaction mixture was poured into saturated sodium bicarbonate solution (50 mL) and was extracted into ethyl acetate (100 mL). The organic solution was washed with brine, dried (MgSO4) and the solvent removed under reduced pressure. Chromatography of the residue (silica, 19:1 dichloromethane:methanol) gave the title compound as a white solid (0.036 g, 80%) ... Mp. 235°C (dec); NMR (DMSO) δ.7.82 (1H, d), 7.30-6.90 (11H, m), 6.85 (2H, d), 35 5.88 (1H, m), 4.86 (1H, d), 4.67 (1H, t), 3.67 (1H, m), 3.45 (1H, m), 2.75 (3H, m), 2.60 (1H, m), 2.43 (1H, m), 1.94 (1H, m), 1, 49 (2H, m), 0.73 (3H, d), 0.62 (3H, d); MS: (CI) m/e 478 [M+H]+.

Most are a constitution of the Example 74.

Preparation of (2R.4S.5S.1'S)-5-(6-quinolinylmethyloxy-V 5 (carbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2yl)methyl-6-phenylmethyl-hexanamide

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Using the procedure of Example 34, except substituting (1.00) (6-quinolinylmethyl)-(4-nitrophenyl) carbonate for (4-0.00) picolinyl)-(4-nitrophenyl) carbonate, the title compound was 10 prepared.

Example 75

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The Preparation of (2R, 4S, 5S, 1'S) -5- (benzoyl) amino-4-hydroxy-N
15 (1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-

hexanamide

(butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl[20 **-6-phenylmethyl-hexamide*: [20 **-6-phenylmethyl-hexamide*: [20

 $\mathcal{C}(t)$ 0 % (a) The compound of Example 13(a) (0.11 g, 0.2 mmol),

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together in dichloromethane (4 mL) at ambient temperature for

48hr. The solvent was removed under reduced pressure and the residue chromatographed (silica, 1:1 ethyl acetate:hexane) to yield the title compound as a white solid (0.080 g, 61%).

. - minimal NMR (CDCl₃) 7.53 (2H, d), 7.40-7.04 (11H, m), 6.93 (2H, d),

6.69 (2H, s), 6.59 (1H, d), 6.37 (1H, d), 4.54 (2H, m), 3.68

30 (1H, t), 2.78 (2H, m), 2.66 (2H, m), 2.39 (1H, dd), 2.13 (1H,

mair dm), 1.623(2H, t), 0.87 (9H, s), 0.53 (3H, d), 0.48 (3H, d),

add = 0.024(3H, s), -0.001(3H, s). When a specific for E =

-688 634 . 1.1.1., b. for which a the basis of the basis

(:35 isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide

10.1 (10.080 g, 0.12 mmol) was

ammomium fluoride, 0.16 mL, 0.16 mmol, 1M solution in THF).

25 .

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After stirring at 40°C for 24 hr, the solvent was removed under reduced pressure and the residue was chromatographed (silica, step gradient, 1:1 ethyl acetate:hexane, 9:9:2 ethyl acetate:hexane:methanol) to give the title compound as a white solid (0.051 g, 79%). Mp. 253-6°C; NMR (DMSO-d₆) & 7.99 (1H, d), 7.91 (1H, d), 7.72 (2H, d), 7.50-7.02 (13H, m), 6.94 (2H, s), 4.83 (1H, br), 4.68 (1H, d), 4.14 (1H, m), 3.58 (1H, d), 2.82 (4H, m), 2.49 (1H, m), 1.92 (1H, m), 1.73 (1H, t), 1.40 (1H, m), 0.73 (3H, d), 0.63 (3H, d); MS (ES) m/e 539.2 [M+H]*.

Example 76

Preparation of (2R.4S.5S.1'S)-5-(2-furylcarbonyl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-)
phenylmethyl-hexanamide

Following the procedure of Example 75(a), except using furoyl chloride in place of benzoyl chloride, the title compound was prepared as a white solid (0.019 g, 18%). Mp 212-3°C (dec); NMR(CDCl3/CD3OD) 6.7.46 (1H, s), 7.30-6.88 (12H, m), 6.85 (2H, s), 6.49 (1H, m), 4.48 (1H, d), 4.20 (1H, m), 3.67 (1H, m), 2.96 (4H, m), 2.77 (2H, m), 12.58 (1H, d), 2.07 (1H, m), 1.71 (2H, m), 0.74 (3H, d), 0.65 (3H, d); MS(ES) m/e 528.32 [M+H]⁺.

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Example 77 mas whose bloom

Preparation of (2R.4S.5S.1'S)-5-(4-methoxybenzoyl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenylmethyl-hexanamide

Following the procedure of Example 75(a), except using 4-methoxybenzoyl chloride in place of benzoyl chloride, the title compound was prepared as a white solid (32%). Mp 235-7°C (dec); NMR(CDCl3/CD3OD) & 7.64 (2H, d), 7.22-6.87 (14H, m), 6.80 (2H, m), 4.52 (1H, d), 4.16 (1H, m), 3.81 (3H, s), 3.62 (1H, d), 2.92 (2H, d), 2.72 (2H, m), 2.53 (1H, dd), 1.98 (1H, m), 1.73 (1H, m), 1.63 (1H, m), 0.71 (3H, d), 10.62 (3H, d); MS(ES) m/e 569.4 [M+H]+.

Lyber - Later Language Example 78

Preparation of (2R.4S.5S.1'S)-5-benzylcarbonyl)amino-4-3E.5 (hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenylmethyl-hexamide.

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a) (2R, 4S, 5S, 1'S) -5-benzylcarbonyl) amino-4-t-butyldimethyl siloxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl

10 -hexanamide...ca and a second a second

** [10] ** Following the procedure of Example 75(a), except using the phenylacetyl chloride in place of benzoyl chloride and triethylamine in place of di(isopropyl) ethylamine, the title compound was prepared as a white solid (20%). NMR(CDCl3) δ 15. 7.40-6.75 (19H, m), 5.40 (1H, d), 4.73 (1H, t), 4.41 (1H, q), 3.68 (1H, m), 3.48 (2H, s), 2.96 (1H, dd), 2.69 (1H, m), 2.49 (4H, m), 1.61 (2H, m), 0.92 (6H, t), 0.77 (9H, s), 0.04 (3H, s), 0.00 (3H, s).

isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide
isopropyl-1'-imidazol-2-yl)methyl-hexanamide
isopropyl-1'-imidazol-2-yl)methyl-he

Example 79

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(3H, s).

a) (2R, 4S, 5S, 1'S) -5-(4-acetoxyphenyl) -4-t-butyl dimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenylmethyl-hexanamide. in the hard of the second

The compound of Example 13(a) (0.11 g; 0.27 mmol) was dissolved in dichloromethane (2 mL), and BOP reagent (0.089 g, 0.2 mmol), triethylamine (0.028 mL, 0.2 mmol) and 4acetoxybenzoic acid (0.043 g. 0.24 mmol) were added. stirring at ambient temperature overnight the solvent was removed under reduced pressure. The residue was enchromatographed (silica, 49:1 dichloromethane:methanol) to give the title compound as a white solid (0.11 g, ..78%). NMR (CDCl₃) 8 7.53 (2H, d), 7.28-6.97 (13H, m), 6.83 (1H, d), 6.78 (2H, s), 6.44 (1H, d), 4.54 (2H, m), 3.72 (1H, dd), 2.79 15 (4H, m), 2.49 (1H, dd), 2.24 (3H, s), 2.20 (1H, m), 1.70 (2H, (3H, s), 0.91 (9H, s), 0.66 (3H, d), 0.57 (3H, d), 0.07 (3H, s), (4) (100) Land (40) '0.02 (3H, s).

b) (2R, 4S, 5S, 1'S) -5-(4-hydroxybenzoyl)amino-4-t-butyl - 20 dimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenylmethyl-hexanamide of the South South South to Indongst "

The product from reaction 79(a) (0.11; g,"0.15 mmol) was dissolved in methanol (5 mL) and powdered potassium carbonate (0.12 g, 0.9 mmol) was added. After stirring the suspension 25 vigorously for 2 h, the mixture was filtered and the solvent removed from the filtrate at reduced pressure. Chromatography of the residue (silica, 19:19:2 ethyl acetate:hexane:methanol) gave the title compound as a white solid (0.066 g, 66%). NMR(CDCl3) 8.7.35 (2H, d) 7.24-6.98 (12H, m), 6.67 (4H, m), 6.32 (1H, d), 4.63 (2H, m), 3.76 (1H, dd), 2.78 (4H, m), 2.44)(1H, d), 2.12 (1H, m), 1.64)(2H, m), 0.88 (9H, s), 0.44 (3H, d); 0.32 (3H, d), 0.05 (3H, s), 0.01

c) (2R, 4S, 5S, 1'S) -5-(4-hydroxybenzoyl) amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-hexanamide Following the procedure of Example 75(b), except using the compound of Example 79(b) in place of the compound of

Example 75(a), the title compound was prepared as a white solid (57%). Mp 267-8°C (dec); NMR(CDCl₃/CD₃OD) δ 7.57 (2H, d), 7.33-6.75 (17H, m), 4.48 (1H, d), 4.14 (1H, m), 3.58 (1H, d), 2.90 (2H, m), 2.82 (1H, m), 2.73 (1H, m), 2.53 (1H, dd), 5 2.04 (1H, m), 1.65 (2H, m), 0.73 (3H, d), 0.58 (3H, d); MS (ES) m/e 555.2 [M+H]⁺.

Example 80

Preparation of (2R.4S.5S.1'S)-5-(cinnamovl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-

- hexanamide and A - 17 1 1 1

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Following the procedure of Example 75(a), except using cinnamoyl chloride in place of benzoyl chloride, the title compound was prepared as a white solid (25%). Mp 273°C; NMR(CDCl₃/CD₃OD) δ 7.55-6.91 (19H, m), 6.86 (2H, s), 6.53 (1H, d), 4.37 (1H, d), 4.15 (1H, dt), 3.62 (1H, d), 2.91 (2H, m), 2.78 (2H, m), 2.59 (1H, dd), 2.04 (1H, m), 1.76 (1H, m), 1.65 (1H, m), 0.79 (3H, d), 0.69 (3H, d); MS (ES) m/e 565.2

a Albarto, well but on the out (2) Example 81

Preparation of (2R.4S.5S.1'S)-5-(2-hydroxybenzoyl)amino-4-\color 25. \color \hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6- \color \color \hat{1} \color \hat{1

Following the procedure of Example 79(a), except using 68.8 (2-acetoxybenzoic acid in place of 4-acetoxybenzoic acid, the title compound was prepared (50%). Mp 197°C; NMR (CD3OD) &

30 7.77 (1H, d), 7.42-6.78 (17H, m), 4.62 (1H, d), 4.32 (1H, -1-10x6) (dt), 3.71 (1H, m), 2.94 (2H, m), 2.78 (2H, m), 2.57 (1H, m), 2.03 (1H, m), 1.84 (1H, m), 1.67 (1H, m), 0.82 (3H, d), 0.68 (3H, d); MS (ES), m/e 555.2 [M+H]⁺.

in a Example 82 (a) (a galagia

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Preparation of (2R.4S.5S.1'S)-5-(imidazov1-4-v1-acetv1)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-v1)methv1-6phenylmethyl-hexanamide () H' | (1.3), (a (11) 60.8) 3

Following the procedure of Example 79(a) -79(c), except using (imidazol-4-yl) acetic acid in place of 4-acetoxy benzoic acid, the title compound was prepared.

Fig. 1 Example 83 Jacon Francisco Of

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-carbomethoxyethylimidazol-2v1) lmethv1-6-phenv1-2-phenvlmethv1-hexanamide menaic

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a) (1S) 1-carbobenzyloxyamino-1-isopropyl-1-[(42)(Ecarbomethoxyethylene) imidazol-2-yl)]methane (((

The compound of Example 27(b) (100 mg, 0.33 mmol); lithium chloride (28 mg, 0.66 mmol) and the state of the trimethylphosphonoacetate (61 mg, 0.33 mmol) were dissolved in anhydrous acetonitrile (2 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (55 mg, 0.36 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silicaa, 2% methanol/ dichloromethane to afford the title compound (72 mg; 61%). NMR(CDCl3) δ 7.60-7.10 (6H, m), 6.50 (1H, br:s), 6.10 (1H, br s), 5.15-4.95 (2H, m), 4.50 (1H, bram), 63.75 (3H, s), 2.30 (1H, br m), 1.10-0.80 (6H, m); MS m/e 358:2"[M+H]+.;

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b) (1S)-1-amino-1-isopropyl-1-(4-carbomethoxyethylimidazol-2yl)methane .

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Following the procedure of Example 1(b); (except substituting the compound of Example 82(a) for the compound of Example 1(a), the title compound was prepared. NMR(CDCl3) δ 6.65 (1H, s), 4.40 (2H, br s), 3.82 (1H, d, J=3 Hz), 3.65 (3H, s), 2.90-2.55 (4H, m), 2.05 (1H, m), 0.90 (6H, d; J=3Hz).

- c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-carbomethoxyethylimidazol-2yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide
- 5 Following the procedure of Example 1(c) except using the compound of Example 82(b), the title compound was prepared. NMR(CDCl3) δ 7.35-6.90 (12H, m), 6.55 (1H, s), 4.75 (1H, d, J=4 Hz), 4.45 (1H, m) 3.95 (1H, m), 3.70 (3H, s), 2.90-2.40 (9H, m), 1.90-1.60 (2H, m), 1.38 (9H, s), 10 0.90-0.70 (15H, m), 0.10 (6H, d, J=2 Hz).
- d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N[1'-isopropyl-1'-(4-carbomethoxyethylimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide.
- 15 Following the procedure of Example of 9(d) except using the compound of Example 83(c), the title compound was prepared. NMR(CDCl3) δ 7.30-6.90 (10H, m), 6.55 (1H, s), 5.00 (1H, d, J=4 Hz), 4.45 (1H, m), 3.70 (3H, s), 2.95-2.50 (9H, m), 2.25 (1H, m), 1.80-1.60 (2H, m), 0.85 (9H, s), 0.70 (6H, d, J=3 Hz); MS m/e 621.4 [M+H]⁺.

Example 84

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-425 hydroxy-N-[1'-isopropyl-1'-(4-carboxamidoimidazol-2yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

; (a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-[(4-

(hydrazinocarbonyl)imidazol-2-yl)]methane

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30 Anhydrous hydrazine (47 μL, 1.5 mmol) was added to a solution of the compound of Example 26(b) (100 mg, 0.30 mmol) in anhydrous methanol. The resulting mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate 35 and 10% aqueous Na₂CO₃ and the organic extract was dried over Na₂CO₃ and evaporated under reduced pressure. The residue was purified by flash chromatography (silica, 4%

methanol/dichloromethane) to afford the title compound (52

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mg, 52%). NMR(CD3OD) δ 7.50 (1H, s), 7.30-7.20 (5H, m), 5.00-4.90 (2H, m), 4.45 (1H, d, J=6 Hz), 2.10 (1H, br m), 0.95-0.75 (6H, m); MS m/e 332.2 [M+H]⁺

b) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-[(4azidocarbonyl)imidazol-2-yl]methane

The compound of Example 83(a) was dissolved in 2N HCl (1 mL) and glacial acetic acid (0.2 mL) and cooled in an ice bath. A solution of sodium nitrite (11 mg, 0.16 mmol) in H2O (200 μL) was added dropwise. The reaction mixture was stirred for 0.5 h, neutralized with cold concentrated ammonium hydroxide and extracted with ethyl acetate. The organic extract was dried over Na₂CO₃ and the solvent removed in vacuo to yield the title compound (54mg, 100%). NMR(CDCl₃) δ 7.75 (1H, s), 7.35-7.20 (5H, m), 5.20-5.00 (2H, m), 4.62 (1H, br m), 2.60 (1H br m), 1.10-0.80 (6H, m); IR 2123cm⁻¹ (CON₃).

c) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4-(1-1)) carboxamidoimidazol-2-yl)methane

The compound of Example 83(b) was dissolved in 2 mL of ethyl acetate and stirred with of concentrated ammonium hydroxide (1 mL) at 0°C for 0.5 h, then at room temperature overnight. The reaction mixture was diluted with H2O, extracted with ethyl acetate, and dried over Na₂CO₃. The solvent was removed in vacuo and the residue was purified by flash chromatography (silica, 4% methanol/ dichloromethane) to afford the title compound (50mg, 100%). NMR(CDCl₃) & 7.45 (1H, s), 7.25-7.10 (5H, m), 5.00-4.85 (2H, m), 4.35 (1H, d, J=3 Hz), 2.00 (1H, br m), 0.90-0.70 (6H, m); MS m/e 317.2 [M+H]⁺.

d) (1S)-1-amino-1-isopropyl-1-(4-carboxamidoimidazol-2-yl)methane.

Following the procedure of Example 1(b), except substituting the compound of Example 83(c) for the compound of Example 1(a), the title compound was prepared. NMR(CDCl3)

Example 85

δ 7.45 (1H, s), 3.47 (1H, d, J=3 Hz), 1.80 (1H, br m), 0.75-0.60 (6H, m).

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e) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t
5 butyldimethylsiloxy-N-[1'-isopropyl-1'-(4
carboxamidoimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-

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hexanamide substitute in

Following the procedure of Example 1(c), except using the compound of Example 83(d), the title compound was 10 prepared. NMR(CDCl3) δ 7.50 (1H, s), 7.45-6.90 (11H, m), 6.25 (1H, d, J=4 Hz), 4.50 (1H, d, J=6Hz), 4.10 (1H, br m), 3.60 (1H, m), 2.90-2.40 (5H, m), 1.90 (1H, br m), 1.70-1.50 (2H, br m), 1.35 (9H, s), 0.90 (9H, s), 0.70-0.60 (6H, m), 0.10 (6H, m).

- f) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4-carboxamidoimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide
- Following the procedure of Example 9(d) except using the compound of Example 83(e) the title compound was prepared.

 NMR(CD30D) δ 7.45 (1H, s), 7.25-6.85 (10H, m), 4.50 (1H, d, J=6 Hz), 4.10 (1H, m), 3.60 (1H, m), 2.85-2.50 (5H, m), 2.00 (1H, br m), 1.80-1.50 (2H, m), 1.30 (9H, s), 0.80-0.65 (6H, m); MS m/e 578.2 [M+H]⁺.

- **25** (2010年) 西南北 (22 July 20 19 July

Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl)-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide

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a) (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-t-butyldimethyl-siloxy-5-Lthioureido-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-W hexanamide

A solution of benzoyl isothiocyanate (prepared from ammonium thiocyanate (147 mg, 1.93 mmol) and benzoyl chloride (257 mg, 1.84 mmol) in of acetone (10 mL) according to the

procedure of J. Amer. Chem. Soc., 56, 1408 (1934)) was treated with a solution of (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-tbutyldimethylsiloxy-5-amino-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide (1.0 g, 1.83 mmol) in acetone. After 20 min at 23°C, the solvent was evaporated, and the residue was dissolved in diethyl ether. The ether extract was washed with water, dried, and the solvent was evaporated. This residue was dissolved in of MeOH (25 mL), treated with 2.5N NaOH (0.1 mL) and heated to 50°C for 30 min. The solvent was evaporated, and the residue was dissolved in EtOAc. The organic solution was washed with water, dried, and the solvent evaporated. The residue was chromatographed (silica, 5% MeOH/CHCl3) to yield the title compound (520 mg, 47%). NMR (DMSO) $\delta \cdot 7.80^{\circ} (1H_{\odot}) d = 7.35$ (1H, d), 6.70-7.20 (15H, m), 4.69 (1H, t), 4.54 (1H, m), 3.78 (1H, m), 2.72-2.86 (3H, m), 2.54 (1h, dd), 2:42 (1H, dd), 2.04 (1H, m), 1.82 (1H, m), 1.30 (1H, m), 0.92 (9H, s), 0.86 (3H, d), 0.74 (3H, d), 0.15 (6H, d). (1, 88 (8), 48) group to the world that it can believe believe to the

20 b) dimethylformamidino derivative of (2R, 4S, 5S, 1'S)-2phenylmethyl-4-dimethyl-t-butyl silyloxy-5-thioureido-6phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl)) methyl-hexanamide

A solution of the compound of Example 85(a) (122 mg, 0.2 mmol) and dimethylformamide dimethylacetal (26 mg, 0.22 mmol) in CHCl₃ (2 mL) was stirred at 23°C for 16 h. The solvent and excess reactant was removed under high vacuum, and the residue was chromatographed (Florisil®, 2* MeOH/CHCL₃) to yield the title compound (100 mg, 76*). NMR(CDCl₃) & 8.82 (1H, s), 7.05-7.40 (12H, m), 6.76 (1H, br s), 6.60 (1H, d),

30 5.32 (1H, m), 4.66 (1H, dd), 3.88 (1H, dd), 3.14 (3H, s), 3.05 (3H, s), 2.70-3.04 (4H, m), 2.40 (2H, m), 1.68 (2H, m), 1.00 (9H, s), 0.80 (6H, dd), 0.14 (6H, d).

c). (2R,4S, 5S, 1'S)-2-phenylmethyl-4-dimethyl-t-butyl
silyloxy-5-(5-(1-oxopropyl)-2-thiazolyl)aminoj-6-phenyl-N(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide

A solution of the compound of Example 85(b) (100 mg, 0.15 mmol), 1-bromo-2-butanone (25 mg, 0.165 mmol), and

triethylamine (33 mg, 0.165 mmol) in acetonitrile (10 mL) was heated at 80°C for 3.5 h. The solvent was evaporated, and the residue shaken with a mixture of diethyl ether and aqueous NaHCO3... The ether was seperated, washed with water, 5. dried, and the solvent was evaporated. The residue was recrystallized from a mixture of CHCl3 and hexane to yield the title compound (59 mg, 57%). NMR(CDCl3) & 7.75 (1H, s), eq. 7.02-7.385(10H, m), 6.881(2H, m), 6.80 (1H, br s), 6.70 (1H, d), 6.60 (1H, d), 4.62 (1H, t), 3.96 (1H, m), 3.78 (1H, t), 2.82 (3H, m), 2.72 (2H, q), 2.54 (2H, m), 2.20 ((1H, m), 2.04 (1H, m), 1.66 (1H, m), 1.15 (3H, t), 0.96 (9H, s), 0.72 (6H, t), 0.10 (6H, d).

oxopropyl) -2-thiazolyl) amino) -6-phenyl-N-(1'-isopropyl-1'-

(imidazo-2-yl))methyl-hexanamide

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A solution of the compound of Example 85(c) (50 mg, 0.07 mmol) in (2 mL) of THF was treated with) of tetrabutyl-ammonium fluoride (0.2 mL, 1N solution in THF) 58°C for 1 h.

- The solvents were evaporated, and the residue dissolved in ether. The ether was washed with water, dried, and the solvent evaporated. The residue was chromatographed (neutral alumina, Activity, V, impurities removed with 2% MeOH/EtOAc, product eluted with 5% MeOH/CHCl3) to yield the title
- 25 compound (22 mg, 55%). NMR (DMSO) & 7.75 (1H, s), 7.66 (1H, d), 6.80-7.30 (13H, m), 4.93 (1H, br s), 4.78 (1H, t), 3.78 (1H, m), 3.68 (1H, dd), 3.00 (1H, dd), 2.92 (1H, dd), 2.86 (1H, m), 2.80-2.90 (1H, br), 2.76 (2H, q), 2.56 (2H, m), 2.12 (1H, m), 1.74 (1H, m), 1.69 (1H, m), 1.20 (3H, t), 0.80 (3H, 30 d), 0.73 (3H, d)

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Example 86

Preparation of (2R.4S.5S.1'S)=2-phenylmethyl-4-hydroxy-5-(5-35 (1-oxopropyl)-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide

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a) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-dimethyl-t-butyl silyloxy-5-(2-thiazolylamino) -6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl)) methyl-hexanamide.

The compound of Example 85(a) (50 mg, 0.08 mmol) in CHCl3 (2 mL) was treated with chloroacetaldehyde (50 mg, 0.64 mmol). After 20 min the solvent and excess reagent were evaporated. The residue was dissolved in EtOAc, washed with aqueous NaHCO3, dried and the solvent evaporated. The residue was chromatographed (Florisil®, 60% EtOAc/hexane) to yield the title compound (42 mg, 83%). NMR(CDCl3) & 7.12-7.30 (10H, m), 7.02 (1H, d), 6.92 (2H, m), 6.82 (1H, br), 6.62 (1H, br), 6.38 (1H, d), 5.86 (1H, br), 4.58 (1H, t), 4.00 (1H, m), 3.86 (1H, m), 2.85 (3H, m), 2.52 (2H, m), 2.26 (1H, m), 2.16 (1H, m), 1.68 (1H, m), 0.98 (9H, s), 0.70 (6H, t), 0.12 (6H, d).

b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-coropyl) -2-thiazolyl) amino) -6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl)) methyl-hexanamide

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Following the procedure of Example 85(d), except substituting the compound of Example 86(a) for the compound of Example 85(c), the title compound was prepared.

NMR(CDCl₃/DMSO) δ 6.80-7.42 (14H, m); 6.40 (2H, m); 5.18 (1H, br), 4.74 (1H, t), 3.70 (1H, m), 3.62 (1H, m), 3.00 (2H, m), 2.88 (2H, m), 2.58 (1H, m), 2.18 (1H, m), 1.80 (2H, m), 1.72 (6H, dd).

Example 87 (1981 1 (6 (1981)

Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(5-propyl-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide

a) (2R,4S,5S,1'S)-2-phenylmethyl-4-t-butyldimethylsilyloxy-5-35/ (5-propyl-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide

A solution of the compound of Example 85(a) (120 mg, 0.2 mmol) in CHCl₃ (5 mL) was treated with 2-bromovaleraldehyde

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(100 mg, 0.6 mmol) and warmed to 60°C for 30 min and 80°C for 5 min. The solvent and excess reagent were removed under reduced pressure. The residue was dissolved in EtOAc, washed with aqueous K2CO3, dried, and the solvent evaporated. The residue was chromatographed (silica, 3% MeOH/CHCl3) to yield the title compound (55 mg, 41%). NMR(CDCl3) & 7.10-7.30 (10H, m), 6.88 (2H, m), 6.72 (1H, br), 6.68 (1H, s), 6.60 (1H, br), 5.60 (1H, br), 4.62 (1H, t), 3.94 (1H, m), 3.78 (1H, t), 2.82 (3H, m), 2.50 (4H, m), 2.26 (1H, m), 2.04 (1H, m), 1.66 (1H, m), 1.55 (2H, sextet), 0.94 (9H, s), 0.92 (3H, t), 0.70 (6H, dd), 0.08 (6H, d).

b). (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(5-propyl-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide.

Following the procedure of Example 85(d), except substituting the compound of Example 87(a) for the compound of Example 85(c), the title compound was prepared. NMR(CDCl₃) δ 7.50 (1H, br), 6.90-7.24 (10H, m), 6.78 (2H, s), 6.60 (1H, s), 6.18 (1H, br), 5.76 (1H, br), 4.60 (1H, t), 3.68 (1H, m), 3.52 (1H, m), 3.05 (1H, dd), 2.95 (2H, m), 2.82 (1H, dd), 2.62 (1H, m), 2.58 (2H, t), 2.32 (1H, m), 1.86 (2H, m), 1.60 (2H, sextet), 0.96 (6H, t), 0.75 (6H, dd).

Example 88

Preparation of (2R.4S.5S.1'S)-5-(nicotinyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide

Following the procedure of Example 75(a), except using nicotinoyl chloride in place of benzoyl chloride, the title compound was prepared as a white solid (43%). Mp 233-4°C (dec); NMR(CDCl₃/CD₃OD) & 8.81 (1H, d), 8.59 (1H, dd), 7.99 (1H, m), 7.35-6.86 (14H, m), 6.79 (2H, s), 4.44 (1H, d), 4.19 (1H, dt), 3.59 (1H, m), 2.90 (2H, d), 2.68 (2H, m), 2.52 (2H, m), 1.96 (1H, m), 1.71 (1H, m), 1.58 (1H, m), 0.70 (3H, d), 0.58 (3H, d); MS(ES) m/e 540.2 [M+H]+.

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The above description fully discloses how to make and
            1997 use the present invention. Howevery the present dinvention is
 because a not limited to the particular embodiments described.
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                                                                              (19, c), 2.82 (25, m), 2.90 (H),
                                                m) 1. 60 (12, a), 1.5 (d.1 ), 10 (41) (d.1 ), (m)
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$$\mathbb{R}^1$$
 \mathbb{R}^2 in \mathbb{R}^3 in \mathbb{R}^3 in \mathbb{R}^3 in \mathbb{R}^4 in $\mathbb{$

of the following the state of t

wherein: [(C-1, -1) %

R¹ and R³ are each independently Q, Q-C₁₋₆alkyl, Q-C₂₋₆alkenyl, Q-C₂₋₆alkynyl or C₁₋₆alkyl substituted by one to five fluorine atoms, each optionally substituted by R²³; Q is H, C₃₋₆cycloalkyl, C₅₋₆cycloalkenyl, Ar or Het

R² is H or OH; R⁴ is R⁶-NR¹¹- or CONR¹¹CHR⁶R⁷; R⁵ is R⁶-NR¹¹- or R¹⁰-NR¹¹-;

 $s = X_{N} I_{R^{0}}$

indicate X is NR11, O or S;

 R^7 is Q, Q-C₁₋₆alkyl or Q-C₂₋₆alkenyl;

R8 and R9 are each independently H, OH, halo, NO2, COR12, CF3, Ar, C1-6alkyl-R15, or R17(R18R19C)m, or together form a

20 fused C2-4alkylene, aryl or heteroaryl moiety;

 R^{10} is A-(B)_n-;

 R^{11} is H or C_{1-4} alkyl;

R¹² is R⁷, OR⁷, NR⁷R¹¹ or an amino acid or amino alcohol; B is an amino acid;

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'G'25'JJW A'IS'H, Ar, Het, R¹⁷(R¹⁸R¹⁹C)m, Ar-W, Het-W or R¹⁷(R¹⁸R¹⁹C)m-W, or phthaloyl each optionally substituted by one to three groups chosen from R¹⁵ or C₁₋₆alkyl-R¹⁵;

W is C=0, OC (=0), NR¹¹C (=0), SC (=0), NR¹¹C (=S), SO₂, $^{\circ}$ NR¹¹SO₂ or P (=0) (OR²²);

C=OR²², CO₂R²², CON(R¹⁶)₂, N(R²²)₂, NHC(=N)NH-A, I, Br, Cl, F, OR¹⁰, or OH, provided that when R¹⁵ is a substituent of the carbon adjacent to W, R¹⁵ is not halogen or OH when W is OC(=0) or NHCO;

35 R16 is H or C1-6alkyl;

R¹⁷, R¹⁸ and R¹⁹ are independently: i) H, R¹⁵ or C₁₋₄alkyl, C₂₋₆alkenyl, phenyl, naphthyl, C₃₋₆cycloalkyl or Het, each optionally substituted by one to three R¹⁵ or R¹⁵-C₁₋₆alkyl groups, or ii) R¹⁷ is as above and (R¹⁸R¹⁹C) are joined together to form a phenyl, naphthyl, C₃₋₆cycloalkyl or Het ring, or iii) R¹⁷ is as above and R¹⁸ and R¹⁹ together are =0;

R²² is H, C₁₋₆alkyl, phenyl or phenyl-C₁₋₄alkyl;

 R^{23} is $-X'-(CH_2)_qNR^{24}R^{25}$, $X''[((CH_2)_rO)_s]R^{26}$,

CH2X"[((CH2)rO)s]R²⁶, or benzofuryl, indolyl, azacycloalkyl, azabicyclo C7-11cycloalkyl or benzopiperidinyl, optionally substituted with C1-4alkyl;

g is 2-5;

s is 1-6 and r is 1-3 within each repeating unit s; X' is CH2, O, S or NH;

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: + (8) · X · 1 · 65.

X" is CH2, NR', O, S, SO or SO2;

R²⁴ and R²⁵ are i) C₁₋₆alkyl, optionally substituted by OH, C₁₋₃alkoxy, or N(R')₂, ii) the same or different and joined together to form a 5-7 member, heterocycle containing up to two additional heteroatoms selected from NR, O, S, SO, SO₂, said heterocycle optionally substituted with C₁₋₄alkyl, iii) aromatic heterocycle, optionally substituted with C₁₋₄alkyl or N(R')₂;

R' is H or C1-4alkyl;

 R^{26} is H, C_{1-4} alkyl, $C(=0)R^{27}$, $C(=0)U[(CH_2)_mO]nR^*$, $P(=0)(OM)_2$, CO_2R^{27} , $C(=0)NR^{27}R^{28}$, where M is a mono or divalent metal ion, and U is NR^* or O_3 .

R²⁷ is C₁₋₆alkyl or Ar, optionally substituted with one or more hydroxy, carboxy, halo, C₁₋₃alkoxy, CONR'₂, NR'₂, CO₂R', SO₂NR'₂, CH₂NR₂, NR'COR', NR'SO₂R', X"[(CH₂)_TO]_SR' or CH₂X"[(CH₂)_TO]_SR';

 R^{28} is H, C_{1-6} alkyl or together with R^{27} forms a.5-7 membered heterocycle or a 6 membered heterocycle containing a heteroatom selected from N, O and S;

m is 1-4; and the commendation of the work with the

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in is 0 or 1; and a green of the light control

or a pharmaceutically acceptable salt thereof. 300 300

2. A compound according to claim 1 wherein:

R1 and R3 are C1-6alkyl, Ar-C1-6alkyl, Ar-C2-6alkenyl,
Ar-C2-6alkynyl, or C1-6alkyl optionally substituted by one to

5 Carrier X. is N-R¹¹; or -trop again to

R4 is CONR¹¹CHR⁶R⁷;

- (Indo an expecte R5 is R10-NR11; e-eye

R⁸ is H, C₁₋₆alkyl, COR¹², NO₂ or Br;

- tyncl0:nov; R9 is H, NO2, Br, COR12, CF3, Ar, C1-6alkyl, or L9 C1-6alkyl-R15, wherein R12 is H, C1-6alkyl, Ar, OC1-6alkyl, NH2, and R15 is OH;

-{ iyi as as ye gat A is H, Het, R17 (R18R19C) m-W or Het-W;

missinBuis absent or Val; so the second of t

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- 15 R¹⁷, R¹⁸ and R¹⁹ are H, or C₁₋₄alkyl, Het or Ar, each with soptionally substituted by one or two R¹⁵ or R¹⁵C₁₋₆alkyl groups, or (R¹⁸R¹⁹C) are joined together to form a phenyl, C₃₋₆cycloalkyl or Het ring; and other systems.

Solvando e garantificamente continual by about on the

3. A compound according to claim 1 wherein R⁴ is CONR¹¹CHR⁶R⁷ and X is N-H.

of Color to their boundary production of the color of the color

- 4. A compound according to claim 3 wherein R⁸ is H and R⁹
 -25] is H or COR¹². Here by the contract the second of the contract that the contract that
 - 5. A compound according to claim 4 wherein R7 is C1-6alkyl.

30 R³ is benzyl, 4-hydroxy-benzyl or phenylpropenyl.

7. A)compound according to claim 3 wherein A is $R^{17}(R^{18}R^{19}C)_m$ -W, and R^{17} , R^{18} and R^{19} are H, or C_{1-4} alkyl, Het

8. A compound according to claim 3 wherein B is absent and A is C_{1-6} alkyloc(=0).

- 9. A compound according to claim 3 wherein W is C=0.
- 10. A compound according to claim 1 wherein the compound is: (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
- amino-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methylhexanamide hydrochloride;
 (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'-(4-aminocarbonyl-thiazo-2yl)]methyl-hexanamide;
- 10 (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(thiazo-2-yl)]methyl
 - hexanamide;
 (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-(1'-imidazo-2-yl) methyl-hexanamide
 - hydrochloride;

 (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-[1'-methyl-1'-(imidazo-2-yl)]&methylhexanamide hydrochloride;

 (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
 - amino-6-phenyl-N-[1'-benzyl-1'-(imidazo-2-yl)]methylhexanamide hydrochloride;
 (2R, 4S, 5S, 1'S)-5-(carbobenzyloxy)amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide;
- 25 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4, 5-dimethyl) imidazol-2-yl] methyl-6-phenyl-2-phenylmethyl-hexanamide;

 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(N'-methyl) imidazol-2-yl] methyl-6-phenyl-2
 - phenylmethyl-hexanamide;

 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-(3phenylpropargyl) hexanamide;

 (2R, 4S, 5S, 1'S) -5-(isopropoxycarbonyl) amino-4-hydroxy-N-(1'-
 - 35 isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl6 to hexanamide;

```
- (2R, 4S, 5S, 1'S) -5-(benzyloxyethoxycarbonyl) amino-4-hydroxy-N-
phenylmethyl-hexanamide;
       (2R, 4S, 5S, 1'S) -5- (methoxycarbonyl) amino-4-hydroxy-N-(1'-
ings 5 isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
         hexanamide:
         (2R, 4S, 5S, 1'S) -5-(ethoxycarbonyl) amino-4-hydroxy-N-(1'-
      isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
         hexanamide;
   10: (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
        isopropyl-1*-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2-
        propenyl) hexanamide;
         (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
     ...isopropyl-1'-(4-nitroimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide;
    - '1 (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
     ethyl-1:-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
        hexanamide:
    (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
   20 propyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
        hexanamide;
     (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
   isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide;
    25 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
  - 'gas isopropyl-1'-(4,5-dibromoimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide;
    - : (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
        isopropyl-1'-(4-methylimidazol-2-yl)]methyl-6-phenyl-2-
       phenylmethyl-hexanamide;
    -:: (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl);amino-4-hydroxy-N-[1'-
        isopropyl-1'-(4-trifluoromethylimidazol-2-yl)]methyl-6-
       phenyl-2-phenylmethyl-hexanamide;
```

(2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-hydroxy-N-methyl-

N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

phenylmethyl-hexanamide;

```
(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                     isopropyl-1'-(4-carbomethoxyimidazol-2-yl)]methyl-6-phenyl-2-
                                                                                                                                         or , it is to a subject to the first of the state of the 
                   phenylmethyl-hexanamide;
                     (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                  isopropyl-1'-(4-methylcarbonylimidazol-2-yl)]methyl-6-phenyl-
                                                                                                                                                                                                grift to sail are.
                   2-phenylmethyl-hexanamide;
         (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                   isopropyl-1'-(4-isopropylcarbonyl-imidazol-2-yl)]methyl-6-
                                                                                                                                                                                              The forces
                   phenyl-2-phenylmethyl-hexanamide;
                     (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
 10
                  isopropyl-1'-(4-phenylcarbonyl-imidazol-2-yl)]methyl-6-
                   phenyl-2-phenylmethyl-hexanamide; bitesimin lives with the
                     (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                   isopropyl-1'-(4-formylimidazol-2-yl)]methyl-6-phenyl-2-
                                                                                                                                            grammer and the state of the st
                   phenylmethyl-hexanamide;
 15
                     (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
             isopropyl-1'-(4-(hydroxymethyl)-imidazol-2-yl)]methyl-6-
                  phenyl-2-phenylmethyl-hexanamide;
            . (2R, 4S, 5S, 1'S)-5-((tetrahydrothiopyran-4-yl)oxycarbonyl)-
                  amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
 20
                  phenyl-2-phenylmethyl-hexanamide;
                    (2R, 4S, 5S, 1'S) -5-((tetrahydro-4H-pyran-4-yl)oxycarbonyl)-
            amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
                 phenyl-2-phenylmethyl-hexanamide; and the second of the se
25 (2R, 4S, 5S, 1'S) -5-(4-picolinyloxy) amino-4-hydroxy-N-(1'-
               isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
                                                                                                                                                       "Masa asada hadiba
                  hexanamide;
                   (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
                  isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(4,4,4-
                 trifluorobut-1-yl) hexanamide ; digum (xbd-05,000) and a
            (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                  isopropyl-1'-(4-((1RS)-1-hydroxyethyl)-imidazol-2-yl)]methyl-
                  6-phenyl-2-phenylmethyl-hexanamide; and and the second
                  (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-(1-
                 methyl)propyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-
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phenylmethyl-hexanamide:

```
: (2R, 4S, 5S, 1'S) -5-(propylaminocarbonyl) amino-4-hydroxy-N-[1'-
                     isopropyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-
                    hexanamide;
                                                                         men with a visiter.
         ..... (2R, 4S, 5S, 1'S) -5- (4-hydroxybutanoyl) amino-4-hydroxy-N-(1'-
                     isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
                    phenylmethylhexanamide; ....
                     (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(benzyloxy-
              carbonyl) valylamino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-
                    yl) methyl-hexanamide;
      v. 10 v. (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(N-acetylvalyl) -
                   amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-yl) methyl-
                    hexanamide;
                     (2R, 4S, 5S, 1'S) -5-[(imidazol-2-yl)methyloxycarbonyl]amino-4-
      -: x: hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-
                   phenylmethyl-hexanamide;
    v = 10 (2R; 4S, 5S, 1'S, 1"RS) -5-((1"-(imidazol-2-yl)-2"-methyl)-
                    propyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
                    imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide;
     (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-
     20 // isopropyl-1!-(4-(imidazol-2-yl)imidazol-2-yl)]methyl-6-
· ·· i) -Gegrphenyl-2-phenylmethyl-hexanamide;
    tobro and (2R, 4S, 5S, 1'S) -5- (1-oxo-thian-4-yl) oxycarbonyl) amino-4-
        ** hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
         15 Trphenylmethylhexanamide; The transfer of the control of the co
        25 (2R, 4S, 5S, 1'S) -5- ((tetrahydrosulfonylpyran-4-
                  yl) oxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
                   vl) methyl-6-phenyl-2-phenylmethylhexanamide;
              (2R, 4S, 5S, 1'S) -5- ((1, 1-dimethyl-2-(benzyloxycarbonyl-
   white englycyloxy) ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
      "[30 @imidazol-2-yl] methyl-6-phenyl-2-phenylmethyl-hexanamide
                   hydrochloride salt; test ( yes - ker shell a fell type of the
                    (2R, 4S, 5S, 1'S)-5-((1, 1-dimethyl-2-glycyloxy) ethoxycarbonyl)-
                 -amino-4-hydroxy-N-(1.'-isopropyl-1.'-imidazol-2-yl)methyl-6-
         aphenyl-2-phenylmethyl-hexanamidedihydrochloridesalt;
           35 o/(2R, 4S, 5S, 1'S) -5-((1-acetyl) amino-4-hydroxy-N-(1'-isopropyl-
                  · 1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide;
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(i

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(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
      isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-(4-9-45
      benzyloxyphenylmethyl)hexanamide;
                                               in tanka det
      (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
      isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-(4-6-3-3-
      hydroxyphenylmethyl) hexanamide; म् अवनुस्त्रवृति मुख्य नेद्वी प्रवासिक
       (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-hydroxy-2-1;
      phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2-
                                      (statements tell patiess )
       yl]methyl-hexanamide;
(2R, 4S, 5S, 1'S) -5-((isopropylthiol) carbonyl) -amino-4-hydroxy-
      2-phenylmethyl-6-phenyl-N-[1-isopropyl-1'-imidazol-2-
      yl]methyl-hexanamide;
       (2R, 4S, 5S, 1'S) -5-[3-(1H-imidazol-2-yl)-3-hydroxy-4-;
      methylpentylamido]-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
      yl)methyl-6-phenyl-2-phenylmethyl-hexanamide; a sign
      (2R, 4S, 5S, 1'S) -5-[(4-methoxyphenoxy)carbonyl]amino-4-hydroxy-
      N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
      2R, 4S, 5S, 1'S) -5-(t-butylaminocarbonyl) amino-4-hydroxy-N-(1'-
  20 isopropyl-1'-imidazol-2-y1)methyl-6-phenylmethyl-hexanamide;
       (2R, 4S, 5S, 1'S)-5-(methylaminocarbonyl)-amino-4-hydroxy-N-(1'-
      · isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
       (2R, 4S, 5S, 1'S)-5-phenylaminocarbonyl) amino-4-hydroxy-N-(1'-
      isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
      (2R, 4S, 5S, 1'S) -5-N-(propylaminocarbonyl) amino-4-hydroxy-N-
  (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
                      and the west great order one growing matter
      hexamide;
       (2R, 4S, 5S, 1'S) -5-(n-propylaminothiono) amino-4-hydroxy-N-
       (1'isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-hexamide;
      2R, 4S, 5S, 1'S) -5-(isopropylaminocarbonyl) -amino-4-hydroxy-N-
       (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
      hexamide; A. M. G. N. William H. William A. (1977) A. (1977) A. (1977)
      (2R, 4S, 5S, 1'S) -5- (aminocarbonyl) amino-4-hydroxy-N-(1'-
      isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
 35 (2R, 4S, 5S, 1'S) -5-(6-quinolinylmethyloxy-carbonyl)amino-4-
   hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
      phenylmethyl-hexanamide;
```

```
(2R, 4S, 5S, 1'S) -5- (benzoyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
         imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
          (2R, 4S, 5S, 1'S) -5-(2-furylcarbonyl) amino-4-hydroxy-N-(1'-
     isopropyl-1'mimidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
 11- (2R, 4S, 5S, 1'S) -5- (4-methoxybenzoyl) amino-4-hydroxy-N-(1'-
         .isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
         (2R, 4S, 5S, 1'S) -5-benzylcarbonyl) amino-4-hydroxy-N-(1'-
      munisopropyl-1!-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
      (2R, 4S, 5S, 1'S)-5-(4-hydroxybenzoyl) amino-4-hydroxy-N-(1'-
         isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
         (2R, 4S, 5S, 1'S) -5- (cinnamoyl) amino-4-hydroxy-N-(1'-isopropyl-
     1 - imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
         (2R, 4S, 5S, 1'S) -5- (2-hydroxybenzoyl) amino-4-hydroxy-N-(1'-
         isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
VIH 15% (2R, 4S, 5S, 1'S)-5-(imidazoyl-4-yl-acetyl)amino-4-hydroxy-N-
 . ..o Jun(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
         hexanamide;
                               and the state of the state of
         (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
      socisopropyl-17-(4-carbomethoxyethylimidazol-2-yl)]methyl-6-
    20 phenyl-2-phenylmethyl-hexanamide; and
         (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
         isopropyl-1'-(4-carboxamidoimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide;
         (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl)-2-
        thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
        yl))methyl-hexanamide;
         (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl) -2-
        thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
'11 how 'yl)) methyl-hexanamide;
.f ad: 30 iou (2R, 4S, 5S, 1'S).-2-phenylmethyl-4-hydroxy-5- (5-propyl-2-
        thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
        yl))methyl-hexanamide; and Jumpe' is become on the 1810 to
         (2R, 4S, 5S, 1'S)-5-(nicotinyl)amino-4-hydroxy-N-(1'-isopropyl-
        1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide.
```

11. A compound according to claim 1 which is (2R, 4S, 5S, 1'S) -. 5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4-

12. A compound according to claim 1 which is (2R, 4S, 5S, 1'S)
5 2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) -amino-6-phenyl
N-(1'-isopropyl-1'-(imidazo-2-yl)) methyl-hexanamide.

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according to Claim 1 and a pharmaceutically (acceptable carrier.

and the control of th

14. A pharmaceutical formulation comprising a compound according to Claim 1 and an oil, 3 -2 - (3) (3)

15 15. A method of treating disease states associated with HIV - infection comprising administering an effective amount of a compound according to Claim 1.

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16. The use of a compound according to Claim 1 in the manufacture of a medicament.

The Control of the State of the product of the State of t

17. A compound of the formula: A seal of a personal

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was a Combined a liver will

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wherein Pr2 is an amino protecting group, and R7 , R8 and R9 are as defined in Claim 1 with any greactive groups protected.

in a company of the gravest configuration and

30 18. A compound of formula: as to be the wardy the markly

The continue product years the line is

wherein:

R₁ and R₃ are each independently C₁₋₆alkyl,
ArrC₁₋₆alkyl, Het-C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₂₋₆alkenyl,
Het-C₂₋₆alkenyl, C₃₋₆cycloalkyl-C₁₋₆alkyl or
C₃₋₆cycloalkenyl-C₁₋₆alkyl;

E.R2cis.H.or.OH; R. R. L. To . Apr. . 4

wherein:

10

X is NR₁₁, 'O,' or S,

3!R11iis H:or C1_3alkyl;

YURs and Ro are each independently H, OH, halo, acyl,

or substituted alkyl;

Sand wherein:

X is NH, O, or S;

R7 is C1-6alkyl, Ar-C1-6alkyl, Het-C1-6alkyl,

20 C2-6alkenyl, Ar-C2-6alkenyl, Het-C2-6alkenyl,

60 C3_6cycloalkyl-C126 alkyl or C3_6cycloalkenyl-C1_6alkyl;

 R_{10} is a molety. A-(B)_n-, where n = 0 or 1; and B is, independently, an α -amino acid chosen from the group: Ala,

Asn, Cys, Trp, Gly, Gln, Ile, Leu, Met, Phe, Pro, Ser, Thr,

25 Tyr, Val, His, or trifluoroalanine, wherein the amino group of B is bonded to A and the carboxy group of B is bonded to the structure;

A is covalently attached to the amino group of the adjacent residue B or to the amino group of the structure if

- 1) trityl,
- 2) hydrogen,
- to plan (3) The Cilfalkyl, include the con-
 - 4) R14-CO-wherein R14 is:

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A 48

	1- 7:	a)	hydrogen, de pad the grant and grant	
	•: • :	•	C1-6alkyl, únsubstituted or substituted with	h
		;	one or more hydroxyl groups, chlorine atoms	3,
			or fluorine atoms, Priving Looks 19, -60	
. 5		c)	phenyl or naphthyl unsubstituted or	
	,	•	substituted with one or more substituents R	15
			wherein R15 is:	
			i) C ₁₋₄ alkyl, and Alexander	
			ii) halogen, where halogen is F, Cl, Br or	•
10.	. •	. ,	The second of th	
			iii) hydroxyl,	
•			iv) nitro, statement	
			v) C1-3alkoxy, or the old a	•
			vi) -CO-N(R16)2 wherein R16 is,	
15	: · •		independently, H or C1-4alkyl; or	
		d)	a 5-7 member heterocycle such as pyridyl,	
	-		furyl, or benzisoxazolyl;	
	5)	phth	naloyl wherein the aromatic ring is	
			ubstituted or substituted with one or more	
20		subs	tituents R ₁₅ ;	
	6)	R17 (R18R19C) m-CO- wherein $m = 1-3$ and R17, R18,	€,
			R ₁₉ are independently:	
	ig g		hydrogen, the five the state of	
•		-	chlorine orafluorine; was a gird to a good to	•
25		c)	C1-3alkyl unsubstituted for substituted with	
i di iyi		•	one or more chlorine or fluorine atoms or	
		_	hydroxyl groups, and an all as no amount	
		d)	hydroxyl, and and a sign of the same	
			$\textbf{phenyl}_{\lambda} \textbf{or} . \textbf{naphthyl} . \textbf{unsubstituted} . \textbf{or}_{\mathcal{D}} = \{ g_{ij} \in \mathcal{D}_{ij} \}$	
10 _{(2: 0.3}	1.36	. •	substituted with one or more substituents R1	5,
•	-	•	C1-3alkoxy,	•
		g), ·	a 5-7 member heterocycle, or	•
erio de la compansión de La compansión de la compa		h)	R17, R18, and R19 may be; independently joined	d
•			to form a monocylic, bicyclic, or tricycle	
5			ring system each ring of which is C3-6	
	:	•	cycloalkyl; may ounge to	
	7)		$R_{18}R_{19}C)_{m}$ -W- wherein m = 1-3 and W is OCO or	
		SO ₂ A	und Riz. Rig. and Rig are as defined above.	

except R17, R18, and R19 are not chlorine, fluorine or hydroxyl if they are adjacent to W;

- R20-W-wherein R20 is a 5-7 member heterocycle such as pyridyl, furyl, or benzisoxazolyl;
- 9) R21-W- wherein R21 is phenyl or naphthyl unsubstituted or substituted with one or more substituents R15;
- 10) R17-(R18R19C)m-P(0) (OR22) wherein R22 is C1-4 alkyl or phenyl;
 - 10 11) R₂₀-P O) (OR₂₂)-; or
 - 12) R₂₁-P(O)(OR₂₂)-;

(00 m2) 30 M (v ook 3 M (M (27 ov)

or pharmaceutically acceptable salt thereof.

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INTERNATIONAL SEARCH REPORT

PCT/US92/06047

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	ASSIFICATION OF SUBJECT MATTER		•		
IPC(5)	:COTD 233/64, 263/32, 277/30; A61K 31/415; :Picaso Sco Extra Sheet.	, 31/42, 31/425	•		
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ategory*	Citation of document, with indication, who	ere appropriate, of the relevant passages	Relevant to claim No.		
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Further documents are listed in the continuation of Box C. See patent family annex.					
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INTERNATIONAL SEARCH REPORT

International application No. PCT/US92/06047

A. CLASSIFICATION OF SUBJECT MATTER: US CL:

514/19, 365, 370, 377, 392, 397, 398, 400; 546/175, 278; 548/193, 194, 200, 204, 233, 236, 312.7, 315.1, 328.5, 332.5, 338.1, 338.5

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/19, 365, 370, 377, 392, 397, 398, 400; 546/175, 278; 548/193, 194, 200, 204, 233, 236, 312.7, 315.1, 328.5, 332.5, 338.1, 338.5